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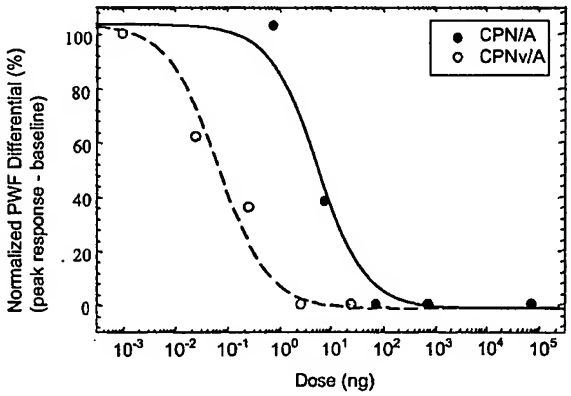

(57) Abstract: A single chain, polypeptide fusion protein, comprising: a non-cytotoxic protease, or a fragment thereof, which protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of a nociceptive sensory afferent; a Targeting Moiety that is capable of binding to a Binding Site on the nociceptive sensory afferent, which Binding Site is capable of undergoing endocytosis to be incorporated into an endosome within the nociceptive sensory afferent; a protease cleavage site at which site the fusion protein is cleavable by a protease, wherein the protease cleavage site is located between the non-cytotoxic protease or fragment thereof and the Targeting Moiety; and a translocation domain that is capable of translocating the protease or protease fragment from within an endosome, across the endosomal membrane and into the cytosol of the nociceptive sensory afferent. Nucleic acid sequences encoding the polypeptide fusion proteins, methods of preparing same and uses thereof are also described.

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Fusion Proteins

This invention relates to non-cytotoxic fusion proteins, and to the therapeutic application thereof as analgesic molecules.

Toxins may be generally divided into two groups according to the type of effect that they have on a target cell. In more detail, the first group of toxins kill their natural target cells, and are therefore known as cytotoxic toxin molecules. This group of toxins is exemplified *inter alia* by plant toxins such as ricin, and abrin, and by bacterial toxins such as diphtheria toxin, and Pseudomonas exotoxin A. Cytotoxic toxins have attracted much interest in the design of "magic bullets" (e.g. immunoconjugates, which comprise a cytotoxic toxin component and an antibody that binds to a specific marker on a target cell) for the treatment of cellular disorders and conditions such as cancer. Cytotoxic toxins typically kill their target cells by inhibiting the cellular process of protein synthesis.

The second group of toxins, which are known as non-cytotoxic toxins, do not (as their name confirms) kill their natural target cells. Non-cytotoxic toxins have attracted much less commercial interest than have their cytotoxic counterparts, and exert their effects on a target cell by inhibiting cellular processes other than protein synthesis. Non-cytotoxic toxins are produced by a variety of plants, and by a variety of microorganisms such as Clostridium sp. and Neisseria sp.

Clostridial neurotoxins are proteins that typically have a molecular mass of the order of 150 kDa. They are produced by various species of bacteria, especially of the genus Clostridium, most importantly *C. tetani* and several strains of *C. botulinum*, *C. butyricum* and *C. argentinense*. There are at present eight different classes of the clostridial neurotoxin, namely: tetanus toxin, and botulinum neurotoxin in its serotypes A, B, C1, D, E, F and G, and they all share similar structures and modes of action.

Clostridial neurotoxins represent a major group of non-cytotoxic toxin molecules, and are synthesised by the host bacterium as single polypeptides that are modified post-translationally by a proteolytic cleavage event to form two polypeptide chains joined together by a disulphide bond. The two chains are termed the heavy chain (H-chain), which has a molecular mass of approximately 100 kDa, and the light chain (L-chain), which has a molecular mass of approximately 50 kDa.

L-chains possess a protease function (zinc-dependent endopeptidase activity) and exhibit a high substrate specificity for vesicle and/or plasma membrane associated proteins involved in the exocytic process. L-chains from different clostridial species or serotypes may hydrolyse different but specific peptide bonds in one of three substrate proteins, namely synaptobrevin, syntaxin or SNAP-25. These substrates are important components of the neurosecretory machinery.

Neisseria sp., most importantly from the species *N. gonorrhoeae*, produce functionally similar non-cytotoxic proteases. An example of such a protease is IgA protease (see WO99/58571).

It has been well documented in the art that toxin molecules may be re-targeted to a cell that is not the toxin's natural target cell. When so re-targeted, the modified toxin is capable of binding to a desired target cell and, following subsequent translocation into the cytosol, is capable of exerting its effect on the target cell. Said re-targeting is achieved by replacing the natural Targeting Moiety (TM) of the toxin with a different TM. In this regard, the TM is selected so that it will bind to a desired target cell, and allow subsequent passage of the modified toxin into an endosome within the target cell. The modified toxin also comprises a translocation domain to enable entry of the non-cytotoxic protease into the cell cytosol. The translocation domain can be the natural translocation domain of the toxin or it can be a different translocation domain obtained from a microbial protein with translocation activity.

For example, WO94/21300 describes modified clostridial neurotoxin molecules that are capable of regulating Integral Membrane Protein (IMP) density present at the cell surface of the target cell. The modified neurotoxin molecules are thus capable of controlling cell activity (e.g. glucose uptake) of the target cell. WO96/33273 and WO99/17806 describe modified clostridial neurotoxin molecules that target peripheral sensory afferents. The modified neurotoxin molecules are thus capable of demonstrating an analgesic effect. WO00/10598 describes the preparation of modified clostridial neurotoxin molecules that target mucus hypersecreting cells (or neuronal cells controlling said mucus hypersecreting cells), which modified neurotoxins are capable of inhibiting hypersecretion from said cells. WO01/21213 describes modified clostridial neurotoxin molecules that target a wide range of different types of non-neuronal target cells. The modified molecules are thus capable of preventing secretion from the target cells. Additional publications in the technical field of re-targeted toxin molecules include: WO00/62814; WO00/04926; US5,773,586; WO93/15766; WO00/61192; and WO99/58571.

The above-mentioned TM replacement may be effected by conventional chemical conjugation techniques, which are well known to a skilled person. In this regard, reference is made to Hermanson, G.T. (1996), Bioconjugate techniques, Academic Press, and to Wong, S.S. (1991), Chemistry of protein conjugation and cross-linking, CRC Press.

Chemical conjugation is, however, often imprecise. For example, following conjugation, a TM may become joined to the remainder of the conjugate at more than one attachment site.

Chemical conjugation is also difficult to control. For example, a TM may become joined to the remainder of the modified toxin at an attachment site on the protease component and/ or on the translocation component. This is problematic

when attachment to only one of said components (preferably at a single site) is desired for therapeutic efficacy.

Thus, chemical conjugation results in a mixed population of modified toxin molecules, which is undesirable.

As an alternative to chemical conjugation, TM replacement may be effected by recombinant preparation of a single polypeptide fusion protein (see WO98/07864). This technique is based on the *in vivo* bacterial mechanism by which native clostridial neurotoxin (i.e. holotoxin) is prepared, and results in a fusion protein having the following structural arrangement:

NH_2 - [protease component] – [translocation component] – [TM] - COOH

According to WO98/07864, the TM is placed towards the C-terminal end of the fusion protein. The fusion protein is then activated by treatment with a protease, which cleaves at a site between the protease component and the translocation component. A di-chain protein is thus produced, comprising the protease component as a single polypeptide chain covalently attached (via a disulphide bridge) to another single polypeptide chain containing the translocation component plus TM. Whilst the WO98/07864 methodology follows (in terms of structural arrangement of the fusion protein) the natural expression system of clostridial holotoxin, the present inventors have found that this system may result in the production of certain fusion proteins that have a substantially-reduced binding ability for the intended target cell.

There is therefore a need for an alternative or improved system for constructing a non-cytotoxic fusion protein.

The present invention addresses one or more of the above-mentioned problems by providing a single chain, polypeptide fusion protein, comprising:

a. a non-cytotoxic protease, or a fragment thereof, which protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus in a nociceptive sensory afferent;

b. a Targeting Moiety that is capable of binding to a Binding Site on the nociceptive sensory afferent, which Binding Site is capable of undergoing endocytosis to be incorporated into an endosome within the nociceptive sensory afferent;

c. a protease cleavage site at which site the fusion protein is cleavable by a protease, wherein the protease cleavage site is located between the non-cytotoxic protease or fragment thereof and the Targeting Moiety; and

d. a translocation domain that is capable of translocating the protease or protease fragment from within an endosome, across the endosomal membrane and into the cytosol of the nociceptive sensory afferent.

The WO98/07864 system works well for the preparation of conjugates having a TM that requires a C-terminal domain for interaction with a Binding Site on a target cell. In this regard, WO98/07864 provides fusion proteins having a C-terminal domain that is "free" to interact with a Binding Site on a target cell. The present inventors have found that this structural arrangement is not suitable for all TMs. One such category of TM is a group of TMs that binds to nociceptive sensory afferents. In more detail, the present inventors have found that the WO 98/07864 fusion protein system is not optimal for TMs requiring a N-terminal domain for interaction with a binding site on a nociceptive sensory afferent. This problem is particularly acute with TMs that require a specific N-terminus amino acid residue or a specific sequence of amino acid residues including the N-terminus amino acid residue for interaction with a binding site on a nociceptive sensory afferent.

In contrast to WO98/07864, the present invention provides a system for preparing non-cytotoxic conjugates, wherein the TM component of the conjugate includes the relevant binding domain in an intra domain or an amino acid sequence located towards the middle (ie. of the linear peptide sequence) of the TM, or preferably located towards the N-terminus of the TM, or more preferably at or near to the N-terminus. The N-terminal domain is capable of binding to a Binding Site on a nociceptive sensory afferent, and the TM preferably has a requirement for a specific and defined sequence of amino acid residue(s) to be free at its N-terminus.

The non-cytotoxic protease component of the present invention is a non-cytotoxic protease, or a fragment thereof, which protease or protease fragment is capable of cleaving different but specific peptide bonds in one of three substrate proteins, namely synaptobrevin, syntaxin or SNAP-25, of the exocytic fusion apparatus in a nociceptive sensory afferent. These substrates are important components of the neurosecretory machinery. The non-cytotoxic protease component of the present invention is preferably a neisserial IgA protease or a fragment thereof or a clostridial neurotoxin L-chain or a fragment thereof. A particularly preferred non-cytotoxic protease component is a botulinum neurotoxin (BoNT) L-chain or a fragment thereof.

The translocation component of the present invention enables translocation of the non-cytotoxic protease (or fragment thereof) into the target cell such that functional expression of protease activity occurs within the cytosol of the target cell. The translocation component is preferably capable of forming ion-permeable pores in lipid membranes under conditions of low pH. Preferably it has been found to use only those portions of the protein molecule capable of pore-formation within the endosomal membrane. The translocation component may be obtained from a microbial protein source, in particular from a bacterial or viral protein source. Hence, in one embodiment, the translocation component is a translocating domain of an enzyme, such as a bacterial toxin or viral protein. The translocation component of the present invention is preferably a clostridial

neurotoxin H-chain or a fragment thereof. Most preferably it is the H_N domain (or a functional component thereof), wherein H_N means a portion or fragment of the H-chain of a clostridial neurotoxin approximately equivalent to the amino-terminal half of the H-chain, or the domain corresponding to that fragment in the intact H-chain.

The TM component of the present invention is responsible for binding the conjugate of the present invention to a Binding Site on a target cell. Thus, the TM component is simply a ligand through which a conjugate of the present invention binds to a selected target cell.

In the context of the present invention, the target cell is a nociceptive sensory afferent, preferably a primary nociceptive afferent (e.g. an A-fibre such as an Aδ-fibre or a C-fibre). Thus, the conjugates of the present invention are capable of inhibiting neurotransmitter or neuromodulator [e.g. glutamate, substance P, calcitonin-gene related peptide (CGRP), and/ or neuropeptide Y] release from discrete populations of nociceptive sensory afferent neurons. In use, the conjugates reduce or prevent the transmission of sensory afferent signals (e.g. neurotransmitters or neuromodulators) from peripheral to central pain fibres, and therefore have application as therapeutic molecules for the treatment of pain, in particular chronic pain.

It is routine to confirm that a TM binds to a nociceptive sensory afferent. For example, a simple radioactive displacement experiment may be employed in which tissue or cells representative of the nociceptive sensory afferent (for example DRGs) are exposed to labelled (e.g. tritiated) ligand in the presence of an excess of unlabelled ligand. In such an experiment, the relative proportions of non-specific and specific binding may be assessed, thereby allowing confirmation that the ligand binds to the nociceptive sensory afferent target cell. Optionally, the assay may include one or more binding antagonists, and the assay may further comprise observing a loss of ligand binding. Examples of this type of

experiment can be found in Hulme, E.C. (1990), Receptor-binding studies, a brief outline, pp. 303-311, In Receptor biochemistry, A Practical Approach, Ed. E.C. Hulme, Oxford University Press.

The fusion proteins of the present invention generally demonstrate a reduced binding affinity (in the region of up to 100-fold) for nociceptive sensory afferent target cells when compared with the corresponding 'free' TM. However, despite this observation, the fusion proteins of the present invention surprisingly demonstrate good efficacy. This can be attributed to two principal features. First, the non-cytotoxic protease component is catalytic – thus, the therapeutic effect of a few such molecules is rapidly amplified. Secondly, the receptors present on the nociceptive sensory afferents need only act as a gateway for entry of the therapeutic, and need not necessarily be stimulated to a level required in order to achieve a ligand-receptor mediated pharmacological response. Accordingly, the fusion proteins of the present invention may be administered at a dosage that is much lower that would be employed for other types of analgesic molecules such as NSAIDS, morphine, and gabapentin. The latter molecules are typically administered at high microgram to milligram (even up to hundreds of milligram) quantities, whereas the fusion proteins of the present invention may be administered at much lower dosages, typically at least 10-fold lower, and more typically at 100-fold lower.

The TM preferably comprises a maximum of 50 amino acid residues, more preferably a maximum of 40 amino acid residues, particularly preferably a maximum of 30 amino acid residues, and most preferably a maximum of 20 amino acid residues.

Opioids represent a preferred group of TMs of the present invention. Within this family of peptides is included enkephalins (met and leu), endomorphins 1 and 2, β-endorphin and dynorphin. Opioid peptides are frequently used in the clinic to modify the activity to nociceptors, and other cells involved in the pain response. As exemplified by the three-step World Health Organisation Analgesic Ladder,

opioids have entry points into the pharmacological treatment of chronic cancer and non-cancer pain at all three stages, underlining their importance to the treatment of pain. Reference to opioids embraces fragments, variants and derivatives thereof, which retain the ability to bind to nociceptive sensory afferents.

The TM of the invention can also be a molecule that acts as an "agonist" at one or more of the receptors present on a nociceptive sensory afferent, more particularly on a primary nociceptive afferent. Conventionally, an agonist has been considered any molecule that can either increase or decrease activities within a cell, namely any molecule that simply causes an alteration of cell activity. For example, the conventional meaning of an agonist would include a chemical substance capable of combining with a receptor on a cell and initiating a reaction or activity, or a drug that induces an active response by activating receptors, whether the response is an increase or decrease in cellular activity.

However, for the purposes of this invention, an agonist is more specifically defined as a molecule that is capable of stimulating the process of exocytic fusion in a target cell, which process is susceptible to inhibition by a protease (or fragment thereof) capable of cleaving a protein of the exocytic fusion apparatus in said target cell.

Accordingly, the particular agonist definition of the present invention would exclude many molecules that would be conventionally considered as agonists. For example, nerve growth factor (NGF) is an agonist in respect of its ability to promote neuronal differentiation via binding to a TrkA receptor. However, NGF is not an agonist when assessed by the above criteria because it is not a principal inducer of exocytic fusion. In addition, the process that NGF stimulates (i.e. cell differentiation) is not susceptible to inhibition by the protease activity of a non-cytotoxic toxin molecule.

The agonist properties of a TM that binds to a receptor on a nociceptive afferent can be confirmed using the methods described in Example 10.

In a preferred embodiment of the invention, the target for the TM is the ORL_1 receptor. This receptor is a member of the G-protein-coupled class of receptors, and has a seven transmembrane domain structure. The properties of the ORL_1 receptor are discussed in detail in Mogil & Pasternak (2001), *Pharmacological Reviews,* Vol. 53, No. 3, pages 381-415.

In one embodiment, the TM is a molecule that binds (preferably that specifically binds) to the ORL_1 receptor. More preferably, the TM is an "agonist" of the ORL_1 receptor. The term "agonist" in this context is defined as above.

The agonist properties of a TM that binds to an ORL_1 receptor can be confirmed using the methods described in Example 10. These methods are based on previous experiments [see Inoue *et al.* 1998 [Proc. Natl. Acad. Sci., 95, 10949-10953]), which confirm that the natural agonist of the ORL_1 receptor, nociceptin, causes the induction of substance P release from nociceptive primary afferent neurons. This is supported by the fact that:

- the nociceptin-induced responses are abolished by specific NK1 receptor (the substance P receptor) antagonists; and

- pre-treatment of the cells with capsaicin (which depletes substance P from small diameter primary afferent neurons) attenuates the nociceptin-induced responses.

Similarly, Inoue *et al.* confirm that an intraplantar injection of botulinum neurotoxin type A abolishes the nociceptin-induced responses. Since it is known that BoNT inhibits the release of substance P from primary afferent neurons (Welch et al., 2000, Toxicon, 38, 245-258), this confirms the link between nociceptin-ORL_1 interaction and subsequent release of substance P.

Thus, a TM can be said to have agonist activity at the ORL_1 receptor if the TM causes an induction in the release of substance P from a nociceptive sensory afferent neuron (see Example 10).

In a particularly preferred embodiment of the invention, the TM is nociceptin - the natural ligand for the ORL_1 receptor. Nociceptin targets the ORL_1 receptor with high affinity. Examples of other preferred TMs include:

Code	Sequence	Ref.	SEQ ID No.
Nociceptin 1-17	FGGFTGARKSARKLANQ	[1]	37,38
Nociceptin 1-11	FGGFTGARKSA	[1]	39,40
Nociceptin [Y10]1-11	FGGFTGARKYA	[1]	41,42
Nociceptin [Y11]1-11	FGGFTGARKSY	[1]	43,44
Nociceptin [Y14]1-17	FGGFTGARKSARKYANQ	[1]	45,46
Nociceptin 1-13	FGGFTGARKSARK	[2]	47,48
Nociceptin [R14K15] 1-17 (also known in this specification as "variant" nociceptin)	FGGFTGARKSARKRKNQ	[3,4]	49,50
Peptide agonist	Peptide agonists from combinatorial library approach	[5]	-

[1] Mogil & Pasternak, 2001, Pharmacol. Rev., 53, 381-415

[2] Maile *et al.*, 2003, Neurosci. Lett., 350, 190-192

[3] Rizzi *et al.*, 2002, J. Pharmacol. Exp. Therap., 300, 57-63

[4] Okada *et al.*, 2000, Biochem. Biophys. Res. Commun., 278, 493-498

[5] Dooley *et al.*, 1997, J Pharmacol Exp Ther. 283(2), 735-41.

The above-identified "variant" TM demonstrates particularly good binding affinity (when compared with natural nociceptin) for nociceptive sensory afferents. This is surprising as the amino acid modifications occur at a position away from the N-terminus of the TM. Moreover, the modifications are almost at the C-terminus of the TM, which in turn is attached to a large polypeptide sequence (i.e. the translocation domain). Generally speaking, a TM-containing fusion protein will demonstrate an approximate 100-fold reduction in binding ability *vis-à-vis* the TM *per se*. The above-mentioned "variant" TM *per se* demonstrates an approximate 3- to 10-fold increase in binding ability for a nociceptive sensory afferent (e.g. via the ORL1 receptor) *vis-à-vis* natural nociceptin. Thus, a "variant" TM-containing fusion might be expected to demonstrate an approximate 10-fold reduction in binding ability for a nociceptive sensory afferent (e.g. via the ORL1 receptor) *vis-à-vis* 'free' nociceptin. However, the present inventors have demonstrated that such "variant" TM-containing fusion proteins demonstrate a binding ability that (most surprisingly) closely mirrors that of 'free' nociceptin – see Figure 14.

In the context of the present invention, the term opioid or an agonist of the ORL_1 receptor (such as nociceptin, or any one of the peptides listed in the table above) embraces molecules having at least 70%, preferably at least 80%, more preferably at least 90%, and most preferably at least 95% homology with said opioid or agonist. The agonist homologues retain the agonist properties of nociceptin at the ORL_1 receptor, which may be tested using the methods provided in Example 10. Similarly, an opioid homologue substantially retains the binding function of the opioid with which it shows high homology.

The invention also encompasses fragments, variants, and derivatives of any one of the TMs described above. These fragments, variants, and derivatives substantially retain the properties that are ascribed to said TMs.

In addition to the above-mentioned opioid and non-opioid classes of TMs, a variety of other polypeptides are suitable for targeting the conjugates of the present invention to nociceptive sensory afferents (e.g. to nociceptors). In this regard, particular reference is made to galanin and derivatives of galanin. Galanin receptors are found pre- and post-synaptically in DRGs (Liu & Hokfelt, (2002), Trends Pharm. Sci., 23(10), 468-74), and are enhanced in expression during neuropathic pain states. Proteinase-activated receptors (PARs) are also a preferred group of TMs of the present invention, most particularly PAR-2. It is known that agonists of PAR-2 induce/ elicit acute inflammation, in part via a neurogenic mechanism. PAR2 is expressed by primary spinal afferent neurons, and PAR2 agonists stimulate release of substance P (SP) and calcitonin gene-related peptide (CGRP) in peripheral tissues

A particularly preferred set of TMs of the present invention includes:

Ligand	**Reference**
Nociceptin	**Guerrini, *et al.***, (1997) J. Med. Chem., 40, pp. 1789-1793
β-endorphin	**Blanc, *et al.***, (1983) J. Biol. Chem., 258(13), pp. 8277-8284
Endomorphin-1; Endomorphin-2	**Zadina, *et al.***, (1997). Nature, 386, pp. 499-502
Dynorphin	**Fields & Basbaum** (2002) Chapter 11, In The Textbook of Pain, Wall & Melzack eds.
Met-enkephalin	**Fields & Basbaum** (2002) Chapter 11, In The Textbook of Pain, Wall & Melzack eds.

Ligand	Reference
Leu-enkephalin	**Fields & Basbaum** (2002) Chapter 11, In The Textbook of Pain, Wall & Melzack eds.
Galanin	**Xu *et al.***, (2000) Neuropeptides, **34** (3&4), 137–147
PAR-2 peptide	**Vergnolle *et al.***, (2001) Nat. Med., 7(7), 821-826

The protease cleavage site of the present invention allows cleavage (preferably controlled cleavage) of the fusion protein at a position between the non-cytotoxic protease component and the TM component. It is this cleavage reaction that converts the fusion protein from a single chain polypeptide into a disulphide-linked, di-chain polypeptide.

According to a preferred embodiment of the present invention, the TM binds via a domain or amino acid sequence that is located away from the C-terminus of the TM. For example, the relevant binding domain may include an intra domain or an amino acid sequence located towards the middle (i.e. of the linear peptide sequence) of the TM. Preferably, the relevant binding domain is located towards the N-terminus of the TM, more preferably at or near to the N-terminus.

In one embodiment, the single chain polypeptide fusion may include more than one proteolytic cleavage site. However, where two or more such sites exist, they are different, thereby substantially preventing the occurrence of multiple cleavage events in the presence of a single protease. In another embodiment, it is preferred that the single chain polypeptide fusion has a single protease cleavage site.

The protease cleavage sequence(s) may be introduced (and/ or any inherent cleavage sequence removed) at the DNA level by conventional means, such as by site-directed mutagenesis. Screening to confirm the presence of cleavage

sequences may be performed manually or with the assistance of computer software (e.g. the MapDraw program by DNASTAR, Inc.).

Whilst any protease cleavage site may be employed, the following are preferred:

Enterokinase	(DDDDK↓)
Factor Xa	(IEGR↓ / IDGR↓)
TEV(Tobacco Etch virus)	(ENLYFQ↓G)
Thrombin	(LVPR↓GS)
PreScission	(LEVLFQ↓GP).

Also embraced by the term protease cleavage site is an intein, which is a self-cleaving sequence. The self-splicing reaction is controllable, for example by varying the concentration of reducing agent present.

In use, the protease cleavage site is cleaved and the N-terminal region (preferably the N-terminus) of the TM becomes exposed. The resulting polypeptide has a TM with an N-terminal domain or an intra domain that is substantially free from the remainder of the conjugate. This arrangement ensures that the N-terminal component (or intra domain) of the TM may interact directly with a Binding Site on a target cell.

In a preferred embodiment, the TM and the protease cleavage site are distanced apart in the fusion protein by at most 10 amino acid residues, more preferably by at most 5 amino acid residues, and most preferably by zero amino acid residues. Thus, following cleavage of the protease cleavage site, a conjugate is provided with a TM that has an N-terminal domain that is substantially free from the remainder of the conjugate. This arrangement ensures that the N-terminal component of the Targeting Moiety may interact directly with a Binding Site on a target cell.

One advantage associated with the above-mentioned activation step is that the TM only becomes susceptible to N-terminal degradation once proteolytic cleavage of the fusion protein has occurred. In addition, the selection of a specific protease cleavage site permits selective activation of the polypeptide fusion into a di-chain conformation.

Construction of the single-chain polypeptide fusion of the present invention places the protease cleavage site between the TM and the non-cytotoxic protease component.

It is preferred that, in the single-chain fusion, the TM is located between the protease cleavage site and the translocation component. This ensures that the TM is attached to the translocation domain (i.e. as occurs with native clostridial holotoxin), though in the case of the present invention the order of the two components is reversed *vis-à-vis* native holotoxin. A further advantage with this arrangement is that the TM is located in an exposed loop region of the fusion protein, which has minimal structural effects on the conformation of the fusion protein. In this regard, said loop is variously referred to as the linker, the activation loop, the inter-domain linker, or just the surface exposed loop (Schiavo *et al* 2000, Phys. Rev., 80, 717-766; Turton *et al*., 2002, Trends Biochem. Sci., 27, 552-558).

In one embodiment, in the single chain polypeptide, the non-cytotoxic protease component and the translocation component are linked together by a disulphide bond. Thus, following cleavage of the protease cleavage site, the polypeptide assumes a di-chain conformation, wherein the protease and translocation components remain linked together by the disulphide bond. To this end, it is preferred that the protease and translocation components are distanced apart from one another in the single chain fusion protein by a maximum of 100 amino acid residues, more preferably a maximum of 80 amino acid residues, particularly preferably by a maximum of 60 amino acid residues, and most preferably by a maximum of 50 amino acid residues.

In one embodiment, the non-cytotoxic protease component forms a disulphide bond with the translocation component of the fusion protein. For example, the amino acid residue of the protease component that forms the disulphide bond is located within the last 20, preferably within the last 10 C-terminal amino acid residues of the protease component. Similarly, the amino acid residue within the translocation component that forms the second part of the disulphide bond may be located within the first 20, preferably within the first 10 N-terminal amino acid residues of the translocation component.

Alternatively, in the single chain polypeptide, the non-cytotoxic protease component and the TM may be linked together by a disulphide bond. In this regard, the amino acid residue of the TM that forms the disulphide bond is preferably located away from the N-terminus of the TM, more preferably towards to C-terminus of the TM.

In one embodiment, the non-cytotoxic protease component forms a disulphide bond with the TM component of the fusion protein. In this regard, the amino acid residue of the protease component that forms the disulphide bond is preferably located within the last 20, more preferably within the last 10 C-terminal amino acid residues of the protease component. Similarly, the amino acid residue within the TM component that forms the second part of the disulphide bond is preferably located within the last 20, more preferably within the last 10 C-terminal amino acid residues of the TM.

The above disulphide bond arrangements have the advantage that the protease and translocation components are arranged in a manner similar to that for native clostridial neurotoxin. By way of comparison, referring to the primary amino acid sequence for native clostridial neurotoxin, the respective cysteine amino acid residues are distanced apart by between 8 and 27 amino acid residues – taken from Popoff, MR & Marvaud, J-C, 1999, Structural & genomic features of

clostridial neurotoxins, Chapter 9, in The Comprehensive Sourcebook of Bacterial Protein Toxins. Ed. Alouf & Freer:

Serotype[1]	Sequence	'Native' length between C-C
BoNT/A1	CVRGIITSKTKS----LDKGYNKALNDLC	23
BoNT/A2	CVRGIIPFKTKS----LDEGYNKALNDLC	23
BoNT/B	CKSVKAPG----------IC	8
BoNT/C	CHKAIDGRS----------LYNKTLDC	15
BoNT/D	CLRLTK----------NSRDDSTC	12
BoNT/E	CKN-IVSVK----------GIRK---SIC	13
BoNT/F	CKS-VIPRK----------GTKAPP-RLC	15
BoNT/G	CKPVMYKNT----------GKSE----QC	13
TeNT	CKKIIPPTNIRENLYNRTASLTDLGGELC	27

[1]Information from proteolytic strains only

The fusion protein may comprise one or more purification tags, which are located N-terminal to the protease component and/ or C-terminal to the translocation component.

Whilst any purification tag may be employed, the following are preferred:

His-tag (e.g. 6 × histidine), preferably as a C-terminal and/ or N-terminal tag
MBP-tag (maltose binding protein), preferably as an N-terminal tag
GST-tag (glutathione-S-transferase), preferably as an N-terminal tag
His-MBP-tag, preferably as an N-terminal tag
GST-MBP-tag, preferably as an N-terminal tag
Thioredoxin-tag, preferably as an N-terminal tag
CBD-tag (Chitin Binding Domain), preferably as an N-terminal tag.

According to a further embodiment of the present invention, one or more peptide spacer molecules may be included in the fusion protein. For example, a peptide spacer may be employed between a purification tag and the rest of the fusion protein molecule (e.g. between an N-terminal purification tag and a protease component of the present invention; and/ or between a C-terminal purification tag and a translocation component of the present invention). A peptide spacer may be also employed between the TM and translocation components of the present invention.

A variety of different spacer molecules may be employed in any of the fusion proteins of the present invention. Examples of such spacer molecules include those illustrated in Figures 28 and 29. Particular mention here is made to GS15, GS20, GS25, and Hx27 – see Figures 28 and 29.

The present inventors have unexpectedly found that the fusion proteins (eg. CPNv/A) of the present invention may demonstrate an improved binding activity for nociceptive sensory afferents when the size of the spacer is selected so that (in use) the C-terminus of the TM and the N-terminus of the translocation component are separated from one another by 40-105 angstroms, preferably by 50-100 angstroms, and more preferably by 50-90 angstroms. In another embodiment, the preferred spacers have an amino acid sequence of 11-29 amino acid residues, preferably 15-27 amino acid residues, and more preferably 20-27 amino acid residues. Suitable spacers may be routinely identified and obtained according to Crasto, C.J. and Feng, J.A. (2000) May, 13(5), pp. 309-312 – see also http://www.fccc./edu/research/labs/feng/limker.html.

In accordance with a second aspect of the present invention, there is provided a DNA sequence that encodes the above-mentioned single chain polypeptide. In a preferred aspect of the present invention, the DNA sequence is prepared as part of a DNA vector, wherein the vector comprises a promoter and terminator.

In a preferred embodiment, the vector has a promoter selected from:

Promoter	Induction Agent	Typical Induction Condition
Tac (hybrid)	IPTG	0.2 mM (0.05-2.0mM)
AraBAD	L-arabinose	0.2% (0.002-0.4%)
T7-*lac* operator	IPTG	0.2 mM (0.05-2.0mM)

The DNA construct of the present invention is preferably designed *in silico*, and then synthesised by conventional DNA synthesis techniques.

The above-mentioned DNA sequence information is optionally modified for codon-biasing according to the ultimate host cell (e.g. *E. coli*) expression system that is to be employed.

The DNA backbone is preferably screened for any inherent nucleic acid sequence, which when transcribed and translated would produce an amino acid sequence corresponding to the protease cleave site encoded by the second peptide-coding sequence. This screening may be performed manually or with the assistance of computer software (e.g. the MapDraw program by DNASTAR, Inc.).

According to a further embodiment of the present invention, there is provided a method of preparing a non-cytotoxic agent, comprising:

a. contacting a single-chain polypeptide fusion protein of the invention with a protease capable of cleaving the protease cleavage site;

b. cleaving the protease cleavage site, and thereby forming a di-chain fusion protein.

This aspect provides a di-chain polypeptide, which generally mimics the structure of clostridial holotoxin. In more detail, the resulting di-chain polypeptide typically has a structure wherein:

a. the first chain comprises the non-cytotoxic protease, or a fragment thereof, which protease or protease fragment is

capable of cleaving a protein of the exocytic fusion apparatus of a nociceptive sensory afferent;

b. the second chain comprises the TM and the translocation domain that is capable of translocating the protease or protease fragment from within an endosome, across the endosomal membrane and into the cytosol of the nociceptive sensory afferent; and

the first and second chains are disulphide linked together.

According to a further aspect of the present invention, there is provided use of a single chain or di-chain polypeptide of the invention, for the manufacture of a medicament for treating, preventing or ameliorating pain.

According to a related aspect, there is provided a method of treating, preventing or ameliorating pain in a subject, comprising administering to said patient a therapeutically effective amount of a single chain or di-chain polypeptide of the invention.

The present invention addresses a wide range of pain conditions, in particular chronic pain conditions. Preferred conditions include cancerous and non-cancerous pain, inflammatory pain and neuropathic pain. The opioid-fusions of the present application are particularly suited to addressing inflammatory pain, though may be less suited to addressing neuropathic pain. The galanin-fusions are more suited to addressing neuropathic pain.

In use, the polypeptides of the present invention are typically employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition may be tailored to the mode of administration. Administration is preferably to a mammal, more preferably to a human.

The polypeptides may, for example, be employed in the form of a sterile solution for intra-articular administration or intra-cranial administration. Spinal injection (e.g. epidural or intrathecal) is preferred.

The dosage ranges for administration of the polypeptides of the present invention are those to produce the desired therapeutic effect. It will be appreciated that the dosage range required depends on the precise nature of the components, the route of administration, the nature of the formulation, the age of the patient, the nature, extent or severity of the patient's condition, contraindications, if any, and the judgement of the attending physician.

Suitable daily dosages are in the range 0.0001-1 mg/kg, preferably 0.0001-0.5 mg/kg, more preferably 0.002-0.5 mg/kg, and particularly preferably 0.004-0.5 mg/kg. The unit dosage can vary from less that 1 microgram to 30mg, but typically will be in the region of 0.01 to 1 mg per dose, which may be administered daily or preferably less frequently, such as weekly or six monthly.

A particularly preferred dosing regimen is based on 2.5 ng of fusion protein (e.g. CPNv/A) as the 1X dose. In this regard, preferred dosages are in the range 1X–100X (i.e. 2.5-250 ng). This dosage range is significantly lower (i.e. at least 10-fold, typically 100-fold lower) than would be employed with other types of analgesic molecules such as NSAIDS, morphine, and gabapentin. Moreover, the above-mentioned difference is considerably magnified when the same comparison is made on a molar basis – this is because the fusion proteins of the present invention have a considerably greater Mw than do conventional 'small' molecule therapeutics.

Wide variations in the required dosage, however, are to be expected depending on the precise nature of the components, and the differing efficiencies of various routes of administration.

Variations in these dosage levels can be adjusted using standard empirical routines for optimisation, as is well understood in the art.

Compositions suitable for injection may be in the form of solutions, suspensions or emulsions, or dry powders which are dissolved or suspended in a suitable vehicle prior to use.

Fluid unit dosage forms are typically prepared utilising a pyrogen-free sterile vehicle. The active ingredients, depending on the vehicle and concentration used, can be either dissolved or suspended in the vehicle.

In preparing administrable solutions, the polypeptides can be dissolved in a vehicle, the solution being made isotonic if necessary by addition of sodium chloride and sterilised by filtration through a sterile filter using aseptic techniques before filling into suitable sterile vials or ampoules and sealing. Alternatively, if solution stability is adequate, the solution in its sealed containers may be sterilised by autoclaving.

Advantageously additives such as buffering, solubilising, stabilising, preservative or bactericidal, suspending or emulsifying agents may be dissolved in the vehicle.

Dry powders which are dissolved or suspended in a suitable vehicle prior to use may be prepared by filling pre-sterilised drug substance and other ingredients into a sterile container using aseptic technique in a sterile area.

Alternatively the polypeptides and other ingredients may be dissolved in an aqueous vehicle, the solution is sterilized by filtration and distributed into suitable containers using aseptic technique in a sterile area. The product is then freeze dried and the containers are sealed aseptically.

Parenteral suspensions, suitable for intramuscular, subcutaneous or intradermal injection, are prepared in substantially the same manner, except that the sterile

components are suspended in the sterile vehicle, instead of being dissolved and sterilisation cannot be accomplished by filtration. The components may be isolated in a sterile state or alternatively it may be sterilised after isolation, e.g. by gamma irradiation.

Advantageously, a suspending agent for example polyvinylpyrrolidone is included in the composition/s to facilitate uniform distribution of the components.

Definitions Section

Targeting Moiety (TM) means any chemical structure associated with an agent that functionally interacts with a Binding Site to cause a physical association between the agent and the surface of a target cell. In the context of the present invention, the target cell is a nociceptive sensory afferent. The term TM embraces any molecule (i.e. a naturally occurring molecule, or a chemically/physically modified variant thereof) that is capable of binding to a Binding Site on the target cell, which Binding Site is capable of internalisation (e.g. endosome formation) - also referred to as receptor-mediated endocytosis. The TM may possess an endosomal membrane translocation function, in which case separate TM and Translocation Domain components need not be present in an agent of the present invention.

The TM of the present invention binds (preferably specifically binds) to a nociceptive sensory afferent (e.g. a primary nociceptive afferent). In this regard, specifically binds means that the TM binds to a nociceptive sensory afferent (e.g. a primary nociceptive afferent) with a greater affinity than it binds to other neurons such as non-nociceptive afferents, and/ or to motor neurons (i.e. the natural target for clostridial neurotoxin holotoxin). The term "specifically binding" can also mean that a given TM binds to a given receptor, for example the ORL_1 receptor, with a binding affinity (Ka) of 10^6 M^{-1} or greater, preferably 10^7 M^{-1} or greater, more preferably 10^8 M^{-1} or greater, and most preferably, 10^9 M^{-1} or greater.

For the purposes of this invention, an agonist is defined as a molecule that is capable of stimulating the process of exocytic fusion in a target cell, which process is susceptible to inhibition by a protease (or fragment thereof) capable of cleaving a protein of the exocytic fusion apparatus in said target cell.

Accordingly, the particular agonist definition of the present invention would exclude many molecules that would be conventionally considered as agonists.

For example, nerve growth factor (NGF) is an agonist in respect of its ability to promote neuronal differentiation via binding to a TrkA receptor. However, NGF is not an agonist when assessed by the above criteria because it is not a principal inducer of exocytic fusion. In addition, the process that NGF stimulates (i.e. cell differentiation) is not susceptible to inhibition by the protease activity of a non-cytotoxic toxin molecule.

The term "fragment", when used in relation to a protein, means a peptide having at least thirty-five, preferably at least twenty-five, more preferably at least twenty, and most preferably at least ten amino acid residues of the protein in question.

The term "variant", when used in relation to a protein, means a peptide or peptide fragment of the protein that contains one or more analogues of an amino acid (e.g. an unnatural amino acid), or a substituted linkage.

The term "derivative", when used in relation to a protein, means a protein that comprises the protein in question, and a further peptide sequence. The further peptide sequence should preferably not interfere with the basic folding and thus conformational structure of the original protein. Two or more peptides (or fragments, or variants) may be joined together to form a derivative. Alternatively, a peptide (or fragment, or variant) may be joined to an unrelated molecule (e.g. a second, unrelated peptide). Derivatives may be chemically synthesized, but will be typically prepared by recombinant nucleic acid methods. Additional

components such as lipid, and/or polysaccharide, and/or polyketide components may be included.

Throughout this specification, reference to the "ORL_1 receptor" embraces all members of the ORL_1 receptor family. Members of the ORL_1 receptor family typically have a seven transmembrane domain structure and are coupled to G-proteins of the G_i and G_0 families. A method for determining the G-protein-stimulating activity of ligands of the ORL_1 receptor is given in Example 12. A method for measuring reduction in cellular cAMP levels following ORL_1 activation is given in Example 11. A further characteristic of members of the ORL_1 receptor family is that they are typically able to bind nociceptin (the natural ligand of ORL_1). As an example, all alternative splice variants of the ORL_1 receptor, are members of the ORL_1 receptor family.

The term non-cytotoxic means that the protease molecule in question does not kill the target cell to which it has been re-targeted.

The protease of the present invention embraces all naturally-occurring non-cytotoxic proteases that are capable of cleaving one or more proteins of the exocytic fusion apparatus in eukaryotic cells.

The protease of the present invention is preferably a bacterial protease (or fragment thereof). More preferably the bacterial protease is selected from the genera *Clostridium* or *Neisseria* (e.g. a clostridial L-chain, or a neisserial IgA protease preferably from *N. gonorrhoeae*).

The present invention also embraces modified non-cytotoxic proteases, which include amino acid sequences that do not occur in nature and/or synthetic amino acid residues, so long as the modified proteases still demonstrate the above-mentioned protease activity.

The protease of the present invention preferably demonstrates a serine or metalloprotease activity (e.g. endopeptidase activity). The protease is preferably specific for a SNARE protein (e.g. SNAP-25, synaptobrevin/VAMP, or syntaxin).

Particular mention is made to the protease domains of neurotoxins, for example the protease domains of bacterial neurotoxins. Thus, the present invention embraces the use of neurotoxin domains, which occur in nature, as well as recombinantly prepared versions of said naturally-occurring neurotoxins.

Exemplary neurotoxins are produced by clostridia, and the term clostridial neurotoxin embraces neurotoxins produced by *C. tetani* (TeNT), and by *C. botulinum* (BoNT) serotypes A-G, as well as the closely related BoNT-like neurotoxins produced by *C. baratii* and *C. butyricum*. The above-mentioned abbreviations are used throughout the present specification. For example, the nomenclature BoNT/A denotes the source of neurotoxin as BoNT (serotype A). Corresponding nomenclature applies to other BoNT serotypes.

The term L-chain fragment means a component of the L-chain of a neurotoxin, which fragment demonstrates a metalloprotease activity and is capable of proteolytically cleaving a vesicle and/or plasma membrane associated protein involved in cellular exocytosis.

A Translocation Domain is a molecule that enables translocation of a protease (or fragment thereof) into a target cell such that a functional expression of protease activity occurs within the cytosol of the target cell. Whether any molecule (e.g. a protein or peptide) possesses the requisite translocation function of the present invention may be confirmed by any one of a number of conventional assays.

For example, Shone C. (1987) describes an *in vitro* assay employing liposomes, which are challenged with a test molecule. Presence of the requisite translocation function is confirmed by release from the liposomes of K^+ and/or

labelled NAD, which may be readily monitored [see Shone C. (1987) Eur. J. Biochem; vol. 167(1): pp. 175-180].

A further example is provided by Blaustein R. (1987), which describes a simple *in vitro* assay employing planar phospholipid bilayer membranes. The membranes are challenged with a test molecule and the requisite translocation function is confirmed by an increase in conductance across said membranes [see Blaustein (1987) FEBS Letts; vol. 226, no. 1: pp. 115-120].

Additional methodology to enable assessment of membrane fusion and thus identification of Translocation Domains suitable for use in the present invention are provided by Methods in Enzymology Vol 220 and 221, Membrane Fusion Techniques, Parts A and B, Academic Press 1993.

The Translocation Domain is preferably capable of formation of ion-permeable pores in lipid membranes under conditions of low pH. Preferably it has been found to use only those portions of the protein molecule capable of pore-formation within the endosomal membrane.

The Translocation Domain may be obtained from a microbial protein source, in particular from a bacterial or viral protein source. Hence, in one embodiment, the Translocation Domain is a translocating domain of an enzyme, such as a bacterial toxin or viral protein.

It is well documented that certain domains of bacterial toxin molecules are capable of forming such pores. It is also known that certain translocation domains of virally expressed membrane fusion proteins are capable of forming such pores. Such domains may be employed in the present invention.

The Translocation Domain may be of a clostridial origin, namely the H_N domain (or a functional component thereof). H_N means a portion or fragment of the H-chain of a clostridial neurotoxin approximately equivalent to the amino-terminal

half of the H-chain, or the domain corresponding to that fragment in the intact H-chain. It is preferred that the H-chain substantially lacks the natural binding function of the H_C component of the H-chain. In this regard, the H_C function may be removed by deletion of the H_C amino acid sequence (either at the DNA synthesis level, or at the post-synthesis level by nuclease or protease treatment). Alternatively, the H_C function may be inactivated by chemical or biological treatment. Thus, the H-chain is preferably incapable of binding to the Binding Site on a target cell to which native clostridial neurotoxin (i.e. holotoxin) binds.

In one embodiment, the translocation domain is a H_N domain (or a fragment thereof) of a clostridial neurotoxin. Examples of suitable clostridial Translocation Domains include:

Botulinum type A neurotoxin	- amino acid residues (449-871)
Botulinum type B neurotoxin	- amino acid residues (441-858)
Botulinum type C neurotoxin	- amino acid residues (442-866)
Botulinum type D neurotoxin	- amino acid residues (446-862)
Botulinum type E neurotoxin	- amino acid residues (423-845)
Botulinum type F neurotoxin	- amino acid residues (440-864)
Botulinum type G neurotoxin	- amino acid residues (442-863)
Tetanus neurotoxin	- amino acid residues (458-879)

For further details on the genetic basis of toxin production in *Clostridium botulinum* and *C. tetani*, we refer to Henderson *et al* (1997) in *The Clostridia: Molecular Biology and Pathogenesis, Academic press.*

The term H_N embraces naturally-occurring neurotoxin H_N portions, and modified H_N portions having amino acid sequences that do not occur in nature and/or synthetic amino acid residues, so long as the modified H_N portions still demonstrate the above-mentioned translocation function.

Alternatively, the Translocation Domain may be of a non-clostridial origin (see Table 4). Examples of non-clostridial Translocation Domain origins include, but not be restricted to, the translocation domain of diphtheria toxin [O=Keefe *et al.*, Proc. Natl. Acad. Sci. USA (1992) 89, 6202-6206; Silverman *et al.*, J. Biol. Chem. (1993) 269, 22524-22532; and London, E. (1992) *Biochem. Biophys. Acta., 1112, pp.25-51*], the translocation domain of *Pseudomonas* exotoxin type A [Prior *et al.* Biochemistry (1992) 31, 3555-3559], the translocation domains of anthrax toxin [Blanke *et al.* Proc. Natl. Acad. Sci. USA (1996) 93, 8437-8442], a variety of fusogenic or hydrophobic peptides of translocating function [Plank *et al.* J. Biol. Chem. (1994) 269, 12918-12924; and Wagner *et al* (1992) *PNAS, 89, pp.7934-7938*], and amphiphilic peptides [Murata *et al* (1992) *Biochem., 31, pp.1986-1992*]. The Translocation Domain may mirror the Translocation Domain present in a naturally-occurring protein, or may include amino acid variations so long as the variations do not destroy the translocating ability of the Translocation Domain.

Particular examples of viral Translocation Domains suitable for use in the present invention include certain translocating domains of virally expressed membrane fusion proteins. For example, Wagner *et al.* (1992) and Murata *et al.* (1992) describe the translocation (i.e. membrane fusion and vesiculation) function of a number of fusogenic and amphiphilic peptides derived from the N-terminal region of influenza virus haemagglutinin. Other virally expressed membrane fusion proteins known to have the desired translocating activity are a translocating domain of a fusogenic peptide of Semliki Forest Virus (SFV), a translocating domain of vesicular stomatitis virus (VSV) glycoprotein G, a translocating domain of SER virus F protein and a translocating domain of Foamy virus envelope glycoprotein. Virally encoded Aspike proteins have particular application in the context of the present invention, for example, the E1 protein of SFV and the G protein of the G protein of VSV.

Use of the Translocation Domains listed in Table (below) includes use of sequence variants thereof. A variant may comprise one or more conservative nucleic acid substitutions and/ or nucleic acid deletions or insertions, with the

proviso that the variant possesses the requisite translocating function. A variant may also comprise one or more amino acid substitutions and/ or amino acid deletions or insertions, so long as the variant possesses the requisite translocating function.

Translocation domain source	Amino acid residues	References
Diphtheria toxin	194-380	**Silverman *et al.***, 1994, J. Biol. Chem. 269, 22524-22532 **London E.**, 1992, Biochem. Biophys. Acta., 1113, 25-51
Domain II of pseudomonas exotoxin	405-613	**Prior *et al.***, 1992, Biochemistry 31, 3555-3559 **Kihara & Pastan**, 1994, Bioconj Chem. 5, 532-538
Influenza virus haemagglutinin	GLFGAIAGFIENGWE GMIDGWYG, and Variants thereof	**Plank *et al.***, 1994, J. Biol. Chem. 269, 12918-12924 **Wagner *et al.***, 1992, PNAS, 89, 7934-7938 **Murata *et al.***, 1992, Biochemistry 31, 1986-1992
Semliki Forest virus fusogenic protein	Translocation domain	**Kielian *et al.***, 1996, J Cell Biol. 134(4), 863-872
Vesicular Stomatitis virus glycoprotein G	118-139	**Yao *et al.***, 2003, Virology 310(2), 319-332
SER virus F protein	Translocation domain	**Seth *et al.***, 2003, J Virol 77(11) 6520-6527
Foamy virus envelope glycoprotein	Translocation domain	**Picard-Maureau *et al.***, 2003, J Virol. 77(8), 4722-4730

Figures

Figure 1 Purification of a LC/A-nociceptin-H_N/A fusion protein

Figure 2 Purification of a nociceptin-LC/A-H_N/A fusion protein

Figure 3 Purification of a LC/C-nociceptin-H_N/C fusion protein

Figure 4 Purification of a LC/A-met enkephalin-H_N/A fusion protein

Figure 5 Comparison of binding efficacy of a LC/A-nociceptin-H_N/A fusion protein and a nociceptin-LC/A-H_N/A fusion protein

Figure 6 *In vitro* catalytic activity of a LC/A-nociceptin-H_N/A fusion protein

Figure 7 Purification of a LC/A-nociceptin variant-H_N/A fusion protein

Figure 8 Comparison of binding efficacy of a LC/A-nociceptin-H_N/A fusion protein and a LC/A-nociceptin variant-H_N/A fusion protein

Figure 9 Expressed / purified LC/A-nociceptin-H_N/A fusion protein family with variable spacer length product(s)

Figure 10 Inhibition of SP release and cleavage of SNAP-25 by CPN-A

Figure 11 Inhibition of SP release and cleavage of SNAP-25 over extended time periods after exposure of DRG to CPN-A

Figure 12 Cleavage of SNAP-25 by CPNv-A

Figure 13 Cleavage of SNAP-25 over extended time periods after exposure of DRG to CPNv-A

Figure 14 CPNv-A fusion-mediated displacement of [3H]-nociceptin binding

Figure 15 Expressed / purified CPNv(Ek)-A product

Figure 16 Cleavage of SNAP-25 by CPNv(Ek)-A

Figure 17 Expressed / purified CPNv-C product

Figure 18 Cleavage of syntaxin by CPNv-C

Figure 19 CPN-A efficacy in the Acute Capsaicin-Induced Mechanical Allodynia model

Figure 20 CPN-A efficacy in the Streptozotocin (STZ)-Induced Peripheral Diabetic Neuropathy (Neuropathic Pain) model

Figure 21 CPNv-A efficacy in the Acute Capsaicin-Induced Mechanical Allodynia model

Figure 22 Expressed / purified LC/A-CPLE-H_N/A product

Figure 23 Expressed / purified LC/A-CPBE-H_N/A product

Figure 24 Expressed / purified CPOP-A product

Figure 25 Expressed / purified CPOPv-A product

Figure 26 *In vitro* SNAP-25 cleavage in a DRG cell model

Figure 27 Expressed / purified CPNv-A-FXa-HT (removable his-tag)

Figure 28 *In vitro* efficacy of LC/A-nociceptin-H_N/A fusion proteins with variable spacer length, as assessed by ligand competition assay

Figure 29 *In vitro* efficacy of LC/A-nociceptin-H_N/A fusion proteins with variable spacer length, as assessed by *in vitro* SNAP-25 cleavage

The Figures are now described in more detail.

Figure 1 - Purification of a LC/A-nociceptin-H_N/A fusion protein

Using the methodology outlined in Example 9, a LC/A-nociceptin-H_N/A fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE (Panel A) and Western blotting (Panel B). Anti-nociceptin antisera (obtained from Abcam) were used as the primary antibody for Western blotting. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

Figure 2 - Purification of a nociceptin-LC/A-H_N/A fusion protein

Using the methodology outlined in Example 9, a nociceptin-LC/A-H_N/A fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column.

Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE (Panel A) and Western blotting (Panel B). Anti-nociceptin antisera (obtained from Abcam) were used as the primary antibody for Western blotting. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

Figure 3 - Purification of a LC/C-nociceptin-H_N/C fusion protein

Using the methodology outlined in Example 9, an LC/C-nociceptin-H_N/C fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE (Panel A) and Western blotting (Panel B). Anti-nociceptin antisera (obtained from Abcam) were used as the primary antibody for Western blotting. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

Figure 4 - Purification of a LC/A-met enkephalin-H_N/A fusion protein

Using the methodology outlined in Example 9, an LC/A-met enkephalin-H_N/A fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples from the purification procedure were assessed by SDS-PAGE. The final purified

material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

Figure 5 - Comparison of binding efficacy of a LC/A-nociceptin-H_N/A fusion protein and a nociceptin-LC/A-H_N/A fusion protein

The ability of nociceptin fusions to bind to the ORL_1 receptor was assessed using a simple competition-based assay. Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of test material in the presence of 1 nM [3H]-nociceptin. The reduction in specific binding of the radiolabelled ligand was assessed by scintillation counting, and plotted in comparison to the efficacy of unlabelled ligand (Tocris nociceptin). It is clear that the LC/A-nociceptin-H_N/A fusion is far superior to the nociceptin-LC/A-H_N/A fusion at interacting with the ORL_1 receptor.

Figure 6 - *In vitro* catalytic activity of a LC/A-nociceptin-H_N/A fusion protein

The *in vitro* endopeptidase activity of the purified LC/A-nociceptin-H_N/A fusion protein was determined essentially as described in Chaddock *et al* 2002, Prot. Express Purif. 25, 219-228. Briefly, SNAP-25 peptide immobilised to an ELISA plate was exposed to varying concentrations of fusion protein for 1 hour at 37°C. Following a series of washes, the amount of cleaved SNAP-25 peptide was quantified by reactivity with a specific antisera.

Figure 7 - Purification of a LC/A-nociceptin variant-H_N/A fusion protein

Using the methodology outlined in Example 9, an LC/A-nociceptin variant-H_N/A fusion protein was purified from *E. coli* BL21 cells. Briefly, the soluble products obtained following cell disruption were applied to a nickel-charged affinity capture column. Bound proteins were eluted with 100 mM imidazole, treated with Factor Xa to activate the fusion protein and remove the maltose-binding protein (MBP) tag, then re-applied to a second nickel-charged affinity capture column. Samples

from the purification procedure were assessed by SDS-PAGE. The final purified material in the absence and presence of reducing agent is identified in the lanes marked [-] and [+] respectively.

Figure 8 - Comparison of binding efficacy of a LC/A-nociceptin-H_N/A fusion protein and a LC/A-nociceptin variant-H_N/A fusion protein

The ability of nociceptin fusions to bind to the ORL_1 receptor was assessed using a simple competition-based assay. Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of test material in the presence of 1nM [3H]-nociceptin. The reduction in specific binding of the radiolabelled ligand was assessed by scintillation counting, and plotted in comparison to the efficacy of unlabelled ligand (Tocris nociceptin). It is clear that the LC/A-nociceptin variant-H_N/A fusion (CPNv-LHA) is superior to the LC/A-nociceptin variant-H_N/A fusion (CPN-LHA) at interacting with the ORL_1 receptor.

Figure 9 - Expressed / purified LC/A-nociceptin-H_N/A fusion protein family with variable spacer length product(s)

Using the methodology outlined in Example 9, variants of the LC/A-CPN-H_N/A fusion consisting of GS10, GS30 and HX27 are purified from *E. coli* cell paste. Samples from the purification of LC/A-CPN(GS10)-H_N/A, LC/A-CPN(GS15)-H_N/A, LC/A-CPN(GS25)-H_N/A, LC/A-CPN(GS30)-H_N/A and LC/A-CPN(HX27)-H_N/A were assessed by SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPBE-A. Top panel: M = benchmark molecular mass markers; S = total *E. coli* protein soluble fraction; FT = proteins that did not bind to the Ni^{2+}-charged Sepharose column; FUSION = fusion protein eluted by the addition of imidazole. Bottom panel: Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni^{2+}-charged Sepharose; Lane 4 = Factor Xa treated material prior to final capture on Ni^{2+}-charged Sepharose;

Lane 5 = purified final material post activation with Factor Xa (5 µl); Lane 6 = purified final material post activation with Factor Xa (10 µl); Lane 7 = purified final material post activation with Factor Xa (20 µl); Lane 8 = purified final material post-activation with Factor Xa + DTT (5 µl); Lane 9 = purified final material post activation with Factor Xa + DTT (10 µl); Lane 10 = purified final material post activation with Factor Xa + DTT (20 µl).

Figure 10 - Inhibition of SP release and cleavage of SNAP-25 by CPN-A

Briefly, primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPN-A for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis and plotted against fusion concentration (dashed line). Material was also recovered for an analysis of substance P content using a specific EIA kit. Inhibition of substance P release is illustrated by the solid line. The fusion concentration required to achieve 50% maximal SNAP-25 cleavage is estimated to be 6.30±2.48 nM.

Figure 11 - Inhibition of SP release and cleavage of SNAP-25 over extended time periods after exposure of DRG to CPN-A

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPN-A for 24 hours. Botulinum neurotoxin (BoNT/A) was used as a control. After this initial exposure, extracellular material was removed by washing, and the cells incubated at 37°C for varying periods of time. At specific time points, cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis and illustrated by the dotted lines. Material was also recovered for an analysis of substance P content using a specific EIA kit. Inhibition of substance P release is illustrated by the solid lines.

Figure 12 - Cleavage of SNAP-25 by CPNv-A

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPNv-A for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis. The fusion concentration required to achieve 50% maximal SNAP-25 cleavage is estimated to be 1.38±0.36 nM.

Figure 13 - Cleavage of SNAP-25 over extended time periods after exposure of DRG to CPNv-A

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPNv-A for 24 hours. CPN-A was used as a control. After this initial exposure, extracellular material was removed by washing, and the cells incubated at 37°C for varying periods of time. At specific time points, cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis.

Figure 14 - CPNv-A fusion-mediated displacement of [3H]-nociceptin binding

The ability of nociceptin fusions to bind to the ORL_1 receptor was assessed using a simple competition-based assay. Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of test material in the presence of 1 nM [3H]-nociceptin. The reduction in specific binding of the radiolabelled ligand was assessed by scintillation counting, and plotted in comparison to the efficacy of unlabelled ligand (Tocris nociceptin). It is clear that the LC/A-nociceptin variant-H_N/A fusion (labelled as CPNv-LHnA) is superior to the LC/A-nociceptin-H_N/A fusion (labelled as CPN-LHnA) at interacting with the ORL_1 receptor.

Figure 15 - Expressed / purified CPNv(Ek)-A product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPNv(Ek)-A. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni^{2+}-charged Sepharose; Lane 4 = purified final material post activation with enterokinase (5 µl); Lane 5 = purified final material post activation with enterokinase (10 µl); Lane 6 = purified final material post activation with enterokinase (20 µl); Lane 7 = purified final material post activation with enterokinase + DTT (5 µl); Lane 8 = purified final material post activation with enterokinase + DTT (10 µl); Lane 9 = purified final material post activation with enterokinase + DTT (20 µl).

Figure 16 - Cleavage of SNAP-25 by CPNv(Ek)-A

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPNv(Ek)-A for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis. CPNv-A as prepared in Example 9 was used for comparison purposes. The percentage cleavage of SNAP-25 by CPNv(Ek)-A (labelled as En activated) and CPNv-A (labelled as Xa activated) are illustrated.

Figure 17 - Expressed / purified CPNv-C product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPNv-C. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 =

purified material following initial capture on Ni^{2+}-charged Sepharose; Lane 4 = Factor Xa treated material prior to final capture on Ni^{2+}-charged Sepharose; Lane 5 = purified material following second capture on Ni^{2+}-charged Sepharose; Lane 6 = final purified material; Lane 7 = final purified material + DTT; Lane 8 = benchmark molecular mass markers.

Figure 18 - Cleavage of syntaxin by CPNv-C

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPNv-C for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-syntaxin to facilitate an assessment of syntaxin cleavage. The percentage of cleaved syntaxin was calculated by densitometric analysis. The fusion concentration required to achieve 50% maximal syntaxin cleavage is estimated to be 3.13±1.96 nM.

Figure 19 - CPN-A efficacy in the Acute Capsaicin-Induced Mechanical Allodynia model

The ability of an LC/A-nociceptin-H_N/A fusion (CPN/A) to inhibit capsaicin-induced mechanical allodynia was evaluated following subcutaneous intraplantar injection in the rat hind paw. Test animals were evaluated for paw withdrawal frequency (PWF%) in response to a 10 g Von Frey filament stimulus series (10 stimuli x 3 trials) prior to recruitment into the study (Pre-Treat); after subcutaneous intraplantar treatment with CPN/A but before capsaicin (Pre-CAP); and following capsaicin challenge post-injection of CPN/A (average of responses at 15' and 30'; CAP). Capsaicin challenge was achieved by injection of 10 µL of a 0.3% solution. Sample dilutions were prepared in 0.5% BSA/saline.

Figure 20 - CPN-A efficacy in the Streptozotocin (STZ)-Induced Peripheral Diabetic Neuropathy (Neuropathic Pain) model

Male Sprague-Dawley rats (250-300 g) are treated with 65 mg/kg STZ in citrate buffer (I.V.) and blood glucose and lipid are measured weekly to define the readiness of the model. Paw Withdrawal Threshold (PWT) is measured in response to a Von Frey filament stimulus series over a period of time. Allodynia is said to be established when the PWT on two consecutive test dates (separated by 1 week) measures below 6 g on the scale. At this point, rats are randomized to either a saline group (negative efficacy control), gabapentin group (positive efficacy control) or a test group (CPN/A). Test materials (20-25 µl) are injected subcutaneously as a single injection (except gabapentin) and the PWT is measured at 1 day post-treatment and periodically thereafter over a 2 week period. Gabapentin (30 mg/kg i.p. @ 3 ml/kg injection volume) is injected daily, 2 hours prior to the start of PWT testing.

Figure 21 - CPNv-A efficacy in the Acute Capsaicin-Induced Mechanical Allodynia model

The ability of an LC/A-nociceptin variant-H_N/A fusion (CPNv/A) to inhibit capsaicin-induced mechanical allodynia was evaluated following subcutaneous intraplantar injection in the rat hind paw. Test animals were evaluated for paw withdrawal frequency (PWF%) in response to a 10 g Von Frey filament stimulus series (10 stimuli x 3 trials) prior to recruitment into the study (Pre-Treat), after subcutaneous intraplantar treatment with CPNv/A but before capsaicin (Pre-CAP), and following capsaicin challenge post-injection of CPNv/A (average of responses at 15' and 30'; CAP). Capsaicin challenge was achieved by injection of 10 µL of a 0.3% solution. Sample dilutions were prepared in 0.5% BSA/saline. These data are expressed as a normalized paw withdrawal frequency differential, in which the difference between the peak response (post-capsaicin) and the baseline response (pre-capsaicin) is expressed as a percentage. With this analysis, it can be seen that CPNv/A is more potent than CPN/A since a lower

dose of CPNv/A is required to achieve similar analgesic effect to that seen with CPN/A.

Figure 22 - Expressed / purified LC/A-CPLE-H_N/A product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPLE-A. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni^{2+}-charged Sepharose; Lane 4 = Factor Xa treated material prior to final capture on Ni^{2+}-charged Sepharose; Lane 5 = purified material following second capture on Ni^{2+}-charged Sepharose; Lane 6 = final purified material; Lane 7 = final purified material + DTT.

Figure 23 - Expressed / purified LC/A-CPBE-H_N/A product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPBE-A. Lane 1 = total *E. coli* protein soluble fraction; Lane 2 = purified material following initial capture on Ni^{2+}-charged Sepharose; Lane 3 = Factor Xa treated material prior to final capture on Ni^{2+}-charged Sepharose; Lane 4 = purified final material post activation with Factor Xa (5 µl); Lane 5 = purified final material post activation with Factor Xa (10 µl); Lane 6 = purified final material post activation with Factor Xa (20 µl); Lane 7 = purified final material post activation with Factor Xa + DTT (5 µl); Lane 8 = purified final material post activation with Factor Xa + DTT (10 µl); Lane 9 = purified final material post activation with Factor Xa + DTT (20 µl); Lane 10 = benchmark molecular mass markers.

Figure 24 - Expressed / purified CPOP-A product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPOP-A. Lane 1 = benchmark molecular mass markers; Lane 2 = purified material following initial capture on Ni^{2+}-charged Sepharose; Lane 3 = Factor Xa treated material prior to final capture on Ni^{2+}-charged Sepharose; Lane 4 = purified material following second capture on Ni^{2+}-charged Sepharose; Lane 5 = purified final material post activation with Factor Xa (5 µl); Lane 6 = purified final material post activation with Factor Xa (10 µl); Lane 7 = purified final material post activation with Factor Xa (20 µl); Lane 8 = purified final material post activation with Factor Xa + DTT (5 µl); Lane 9 = purified final material post activation with Factor Xa + DTT (10 µl); Lane 10 = purified final material post activation with Factor Xa + DTT (20 µl).

Figure 25 - Expressed / purified CPOPv-A product

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPOPv-A. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = purified material following initial capture on Ni^{2+}-charged Sepharose; Lane 4 = Factor Xa treated material prior to final capture on Ni^{2+}-charged Sepharose; Lane 5 = purified final material post activation with Factor Xa (5 µl); Lane 6 = purified final material post activation with Factor Xa (10 µl); Lane 7 = purified final material post activation with Factor Xa (20 µl); Lane 8 = purified final material post activation with Factor Xa + DTT (5 µl); Lane 9 = purified final material post activation with Factor Xa + DTT (10 µl); Lane 10 = purified final material post activation with Factor Xa + DTT (20 µl).

Figure 26 - *In vitro* SNAP-25 cleavage in a DRG cell model

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of GPOPv-A for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis.

Figure 27 - Expressed / purified CPNv-A-FXa-HT (removable his-tag)

Proteins were subjected to SDS-PAGE prior to staining with Coomassie Blue. The electrophoresis profile indicates purification of a disulphide-bonded di-chain species of the expected molecular mass of CPNv-A-FXa-HT. Lane 1 = benchmark molecular mass markers; Lane 2 = total *E. coli* protein soluble fraction; Lane 3 = Factor Xa treated material prior to final capture on Ni^{2+}-charged Sepharose; Lane 4 = purified final material post activation with Factor Xa; Lane 5 = purified final material post activation with Factor Xa + DTT.

Figure 28 - *In vitro* efficacy of LC/A-nociceptin-H_N/A fusion proteins with variable spacer length, as assessed by ligand competition assay

The ability of LC/A-nociceptin-H_N/A fusions of variable spacer length to bind to the ORL_1 receptor was assessed using a simple competition-based assay. Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of test material in the presence of 1 nM [3H]-nociceptin. The reduction in specific binding of the radiolabelled ligand was assessed by scintillation counting, and plotted in comparison to the efficacy of unlabelled ligand (Tocris nociceptin). The upper panel illustrates the displacement characteristics of the GS0, GS20, GS30 and Hx27 spacers, whilst the lower panel illustrates the displacement achieved by the GS10, GS15 and GS25 spaced fusion proteins. It is concluded that the GS0 and GS30 spacers are

ineffective, and the GS10 is poorly effective, at displacing nociceptin from the ORL1 receptor.

Figure 29 - *In-vitro* efficacy of LC/A-nociceptin-H_N/A fusion proteins with variable spacer length, as assessed by *in vitro* SNAP-25 cleavage

Primary cultures of dorsal root ganglia (DRG) were exposed to varying concentrations of CPN-A (of variable spacer length) for 24 hours. Cellular proteins were separated by SDS-PAGE, Western blotted, and probed with anti-SNAP-25 to facilitate an assessment of SNAP-25 cleavage. The percentage of cleaved SNAP-25 was calculated by densitometric analysis. The poorly effective binding characteristics of the GS10 spaced fusion protein (see Figure 28) are reflected in the higher concentrations of fusion required to achieve cleavage of intracellular SNAP-25. GS0 and GS30 spaced fusion proteins were completely ineffective (date not shown). GS15, 20 and 25 spaced fusion proteins were similarly effective.

SEQ ID NOs

SEQ ID1	DNA sequence of the LC/A
SEQ ID2	DNA sequence of the H_N/A
SEQ ID3	DNA sequence of the LC/B
SEQ ID4	DNA sequence of the H_N/B
SEQ ID5	DNA sequence of the LC/C
SEQ ID6	DNA sequence of the H_N/C
SEQ ID7	DNA sequence of the CPN-A linker
SEQ ID8	DNA sequence of the A linker
SEQ ID9	DNA sequence of the N-terminal presentation nociceptin insert
SEQ ID10	DNA sequence of the CPN-C linker
SEQ ID11	DNA sequence of the CPBE-A linker
SEQ ID12	DNA sequence of the CPNvar-A linker
SEQ ID13	DNA sequence of the LC/A-CPN-H_N/A fusion

SEQ ID14 Protein sequence of the LC/A-CPN-H_N/A fusion

SEQ ID15 DNA sequence of the N-LC/A-H_N/A fusion

SEQ ID16 Protein sequence of the N-LC/A-H_N/A fusion

SEQ ID17 DNA sequence of the LC/C-CPN-H_N/C fusion

SEQ ID18 Protein sequence of the LC/C-CPN-H_N/C fusion

SEQ ID19 DNA sequence of the LC/C-CPN-H_N/C (A-linker) fusion

SEQ ID20 Protein sequence of the LC/C-CPN-H_N/C (A-linker) fusion

SEQ ID21 DNA sequence of the LC/A-CPME-H_N/A fusion

SEQ ID22 Protein sequence of the LC/A-CPME-H_N/A fusion

SEQ ID23 DNA sequence of the LC/A-CPBE-H_N/A fusion

SEQ ID24 Protein sequence of the LC/A-CPBE-H_N/A fusion

SEQ ID25 DNA sequence of the LC/A-CPNv-H_N/A fusion

SEQ ID26 Protein sequence of the LC/A-CPNv-H_N/A fusion

SEQ ID27 DNA sequence of the LC/A-CPN[1-11]-HN/A fusion

SEQ ID28 Protein sequence of the LC/A-CPN[1-11]-HN/A fusion

SEQ ID29 DNA sequence of the LC/A-CPN[[Y10]1-11]-HN/A fusion

SEQ ID30 Protein sequence of the LC/A-CPN[[Y10]1-11]-HN/A fusion

SEQ ID31 DNA sequence of the LC/A-CPN[[Y11]1-11]-HN/A fusion

SEQ ID32 Protein sequence of the LC/A-CPN[[Y11]1-11]-HN/A fusion

SEQ ID33 DNA sequence of the LC/A-CPN[[Y14]1-17]-HN/A fusion

SEQ ID34 Protein sequence of the LC/A-CPN[[Y14]1-17]-HN/A fusion

SEQ ID35 DNA sequence of the LC/A-CPN[1-13]-HN/A fusion

SEQ ID36 Protein sequence of the LC/A- CPN[1-13]-HN/A fusion

SEQ ID37 DNA sequence of CPN[1-17]

SEQ ID38 Protein Sequence of CPN[1-17]

SEQ ID39 DNA sequence of CPN[1-11]

SEQ ID40 Protein sequence of CPN[1-11]

SEQ ID41 DNA sequence of CPN[[Y10]1-11]

SEQ ID42 Protein sequence of CPN[[Y10]1-11]

SEQ ID43 DNA sequence of CPN[[Y11]1-11]

SEQ ID44 Protein sequence of CPN[[Y11]1-11]

SEQ ID45 DNA sequence of CPN[[Y14]1-17]

SEQ ID46 Protein sequence of CPN[[Y14]1-17]

SEQ ID47 DNA sequence of CPN[1-13]

SEQ ID48 Protein sequence of CPN[1-13]

~~SEQ ID49 DNA sequence of CPNv (also known as N[[R14K15]1-17])~~

SEQ ID50 Protein sequence of CPNv (also known as N[[R14K15]1-17])

SEQ ID51 DNA sequence of the nociceptin-spacer-LC/A-H_N/A fusion

SEQ ID52 Protein sequence of the nociceptin-spacer-LC/A-H_N/A fusion

SEQ ID53 DNA sequence of the CPN-A GS10 linker

SEQ ID54 DNA sequence of the CPN-A GS15 linker

SEQ ID55 DNA sequence of the CPN-A GS25 linker

SEQ ID56 DNA sequence of the CPN-A GS30 linker

SEQ ID57 DNA sequence of the CPN-A HX27 linker

SEQ ID58 DNA sequence of the LC/A-CPN(GS15)-H_N/A fusion

SEQ ID59 Protein sequence of the LC/A-CPN(GS15)-H_N/A fusion

SEQ ID60 DNA sequence of the LC/A-CPN(GS25)-H_N/A fusion

SEQ ID61 Protein sequence of the LC/A-CPN(GS25)-H_N/A fusion

SEQ ID62 DNA sequence of the CPNvar-A Enterokinase activatable linker

SEQ ID63 DNA sequence of the LC/A-CPNv(Ek)-H_N/A fusion

SEQ ID64 Protein sequence of the LC/A-CPNv(Ek)-H_N/A fusion

SEQ ID65 DNA sequence of the CPNvar-A linker

SEQ ID66 DNA sequence of the LC/C-CPNv-H_N/C fusion (act. A)

SEQ ID67 Protein sequence of the LC/C-CPNv-H_N/C fusion (act. A)

SEQ ID68 DNA sequence of the LC/A-CPLE-H_N/A fusion

SEQ ID69 Protein sequence of the LC/A-CPLE-H_N/A fusion

SEQ ID70 DNA sequence of the LC/A-CPOP-H_N/A fusion

SEQ ID71 Protein sequence of the LC/A-CPOP-H_N/A fusion

SEQ ID72 DNA sequence of the LC/A-CPOPv-H_N/A fusion

SEQ ID73 Protein sequence of the LC/A-CPOPv-H_N/A fusion

SEQ ID74 DNA sequence of the IgA protease

SEQ ID75 DNA sequence of the IgA-CPNv-H_N/A fusion

SEQ ID76 Protein sequence of the IgA-CPNv-H_N/A fusion

SEQ ID77 DNA sequence of the FXa-HT

SEQ ID78 DNA sequence of the CPNv-A-FXa-HT
SEQ ID79 Protein sequence of the CPNv-A-FXa-HT fusion
SEQ ID80 DNA sequence of the DT translocation domain
SEQ ID81 DNA sequence of the CPLE-DT-A
SEQ ID82 Protein sequence of the CPLE-DT-A fusion
SEQ ID83 DNA sequence of the TeNT LC
SEQ ID84 DNA sequence of the CPNv-TENT LC
SEQ ID85 Protein sequence of the CPNV-TeNT LC fusion
SEQ ID86 DNA sequence of the CPNvar-C linker
SEQ ID87 DNA sequence of the LC/C-CPNv-H_N/C fusion (act. C)
SEQ ID88 Protein sequence of the LC/C-CPNv-H_N/C fusion (act. C)

Examples

Example 1 - Preparation of a LC/A and H_N/A backbone clones

The following procedure creates the LC and H_N fragments for use as the component backbone for multidomain fusion expression. This example is based on preparation of a serotype A based clone (SEQ ID1 and SEQ ID2), though the procedures and methods are equally applicable to the other serotypes [illustrated by the sequence listing for serotype B (SEQ ID3 and SEQ ID4) and serotype C (SEQ ID5 and SEQ ID6)].

Preparation of cloning and expression vectors

pCR 4 (Invitrogen) is the chosen standard cloning vector, selected due to the lack of restriction sequences within the vector and adjacent sequencing primer sites for easy construct confirmation. The expression vector is based on the pMAL (NEB) expression vector, which has the desired restriction sequences within the multiple cloning site in the correct orientation for construct insertion (*Bam*HI-*Sal*I-*Pst*I-*Hin*dIII). A fragment of the expression vector has been removed to create a non-mobilisable plasmid and a variety of different fusion tags have been inserted to increase purification options.

Preparation of protease (e.g. LC/A) insert

The LC/A (SEQ ID1) is created by one of two ways:

The DNA sequence is designed by back translation of the LC/A amino acid sequence [obtained from freely available database sources such as GenBank (accession number P10845) or Swissprot (accession locus BXA1_CLOBO) using one of a variety of reverse translation software tools (for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)]. *Bam*HI/*Sal*I recognition sequences are incorporated at the 5' and 3' ends respectively of the sequence, maintaining the correct reading frame. The DNA sequence is screened (using software such as MapDraw, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that are found to be common to those required by the cloning system are removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence containing the LC/A open reading frame (ORF) is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

The alternative method is to use PCR amplification from an existing DNA sequence with *Bam*HI and *Sal*I restriction enzyme sequences incorporated into the 5' and 3' PCR primers respectively. Complementary oligonucleotide primers are chemically synthesised by a supplier (for example MWG or Sigma-Genosys), so that each pair has the ability to hybridize to the opposite strands (3' ends pointing "towards" each other) flanking the stretch of *Clostridium* target DNA, one oligonucleotide for each of the two DNA strands. To generate a PCR product the pair of short oligonucleotide primers specific for the *Clostridium* DNA sequence are mixed with the *Clostridium* DNA template and other reaction components and placed in a machine (the 'PCR machine') that can change the incubation

temperature of the reaction tube automatically, cycling between approximately 94°C (for denaturation), 55°C (for oligonucleotide annealing), and 72°C (for synthesis). Other reagents required for amplification of a PCR product include a DNA polymerase (such as *Taq* or *Pfu* polymerase), each of the four nucleotide dNTP building blocks of DNA in equimolar amounts (50-200 μM) and a buffer appropriate for the enzyme optimised for Mg^{2+} concentration (0.5-5 mM).

The amplification product is cloned into pCR 4 using either, TOPO TA cloning for *Taq* PCR products or Zero Blunt TOPO cloning for *Pfu* PCR products (both kits commercially available from Invitrogen). The resultant clone is checked by sequencing. Any additional restriction sequences which are not compatible with the cloning system are then removed using site directed mutagenesis [for example, using Quickchange (Stratagene Inc.)].

Preparation of translocation (e.g. H_N) insert

The H_N/A (SEQ ID2) is created by one of two ways:

The DNA sequence is designed by back translation of the H_N/A amino acid sequence [obtained from freely available database sources such as GenBank (accession number P10845) or Swissprot (accession locus BXA1_CLOBO)] using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)]. A *Pst*I restriction sequence added to the N-terminus and *Xba*I-stop codon-*Hin*dIII to the C-terminus ensuring the correct reading frame is maintained. The DNA sequence is screened (using software such as MapDraw, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any sequences that are found to be common to those required by the cloning system are removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank

Release 143, 13 September 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

The alternative method is to use PCR amplification from an existing DNA sequence with *Pst*I and *Xba*I-stop codon-*Hin*dIII restriction enzyme sequences incorporated into the 5' and 3' PCR primers respectively. The PCR amplification is performed as described above. The PCR product is inserted into pCR 4 vector and checked by sequencing. Any additional restriction sequences which are not compatible with the cloning system are then removed using site directed mutagenesis [for example using Quickchange (Stratagene Inc.)].

Example 2 – Preparation of a LC/A-nociceptin-H_N/A fusion protein (nociceptin is N-terminal of the H_N-chain)

Preparation of linker-nociceptin-spacer insert

The LC-H_N linker can be designed from first principle, using the existing sequence information for the linker as the template. For example, the serotype A linker (in this case defined as the inter-domain polypeptide region that exists between the cysteines of the disulphide bridge between LC and H_N) is 23 amino acids long and has the sequence VRGIITSKTKSLDKGYNKALNDL. Within this sequence, it is understood that proteolytic activation in nature leads to an H_N domain that has an N-terminus of the sequence ALNDL. This sequence information is freely available from available database sources such as GenBank (accession number P10845) or Swissprot (accession locus BXA1_CLOBO). Into this linker a Factor Xa site, nociceptin and spacer are incorporated; and using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)], the DNA sequence encoding the linker-ligand-spacer region is determined. Restriction sites are then incorporated into the DNA sequence and can be arranged as *Bam*HI-*Sal*I-linker-protease site-nociceptin-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hin*dIII (SEQ ID7). It is important to ensure the correct reading frame is

maintained for the spacer, nociceptin and restriction sequences and that the *Xba*I sequence is not preceded by the bases, TC, which would result on DAM methylation. The DNA sequence is screened for restriction sequence incorporation, and any additional sequences are removed manually from the remaining sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example, GenBank Release 143, 13 September 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

Preparation of the LC/A-nociceptin-H_N/A fusion

In order to create the LC-linker-nociceptin-spacer-H_N construct (SEQ ID13), the pCR 4 vector encoding the linker (SEQ ID7) is cleaved with *Bam*HI + *Sal*I restriction enzymes. This cleaved vector then serves as the recipient vector for insertion and ligation of the LC/A DNA (SEQ ID1) cleaved with *Bam*HI + *Sal*I. The resulting plasmid DNA is then cleaved with *Pst*I + *Xba*I restriction enzymes and serves as the recipient vector for the insertion and ligation of the H_N/A DNA (SEQ ID2) cleaved with *Pst*I + *Xba*I. The final construct contains the LC-linker-nociceptin-spacer-H_N ORF (SEQ ID13) for transfer into expression vectors for expression to result in a fusion protein of the sequence illustrated in SEQ ID14.

Example 3 – Preparation of a nociceptin-LC/A-H_N/A fusion protein (nociceptin is N-terminal of the LC-chain)

The LC/A-H_N/A backbone is constructed as described in Example 2 using the synthesised A serotype linker with the addition of a Factor Xa site for activation, arranged as *Bam*HI-*Sal*I-linker-protease site-linker-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID8). The LC/A-H_N/A backbone and the synthesised N-terminal presentation nociceptin insert (SEQ ID9) are cleaved with *Bam*HI + *Hind*III restriction enzymes, gel purified and ligated together to create a nociceptin-

spacer-LC-linker-H_N. The ORF (SEQ ID15) is then cut out using restriction enzymes *AvaI* + *XbaI* for transfer into expression vectors for expression to result in a fusion protein of the sequence illustrated in SEQ ID16.

Example 4 – Preparation of a LC/C-nociceptin-H_N/C fusion protein

Following the methods used in Examples 1 and 2, the LC/C (SEQ ID5) and H_N/C (SEQ ID6) are created and inserted into the C serotype linker arranged as *Bam*HI-*Sal*I-linker-protease site-nociceptin-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID10). The final construct contains the LC-linker-nociceptin-spacer-H_N ORF (SEQ ID17) for expression as a protein of the sequence illustrated in SEQ ID18.

Example 5 - Preparation of a LC/C-nociceptin-H_N/C fusion protein with a serotype A activation sequence

Following the methods used in Examples 1 and 2, the LC/C (SEQ ID5) and H_N/C (SEQ ID6) are created and inserted into the A serotype linker arranged as *Bam*HI-*Sal*I-linker-protease site-nociceptin-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID7). The final construct contains the LC-linker-nociceptin-spacer-H_N ORF (SEQ ID19) for expression as a protein of the sequence illustrated in SEQ ID20.

Example 6 - Preparation of a LC/A-met enkephalin-H_N/A fusion protein

Due to the small, five-amino acid, size of the met-enkephalin ligand the LC/A-met enkephalin-H_N/A fusion is created by site directed mutagenesis [for example using Quickchange (Stratagene Inc.)] using the LC/A-nociceptin-H_N/A fusion (SEQ ID13) as a template. Oligonucleotides are designed encoding the YGGFM met-enkephalin peptide, ensuring standard *E.coli* codon usage is maintained and no additional restriction sites are incorporated, flanked by sequences complimentary to the linker region of the LC/A-nociceptin-H_N/A fusion (SEQ ID13)

either side on the nociceptin section. The SDM product is checked by sequencing and the final construct containing the LC-linker-met enkephalin-spacer-H_N ORF (SEQ ID21) for expression as a protein of the sequence illustrated in SEQ ID22.

Example 7 - Preparation of a LC/A-β endorphin-H_N/A fusion protein

Following the methods used in Examples 1 and 2, the LC/A (SEQ ID1) and H_N/A (SEQ ID2) are created and inserted into the A serotype β endorphin linker arranged as *Bam*HI-*Sal*I-linker-protease site-β endorphin-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hin*dIII (SEQ ID11). The final construct contains the LC-linker-β endorphin-spacer-H_N ORF (SEQ ID23) for expression as a protein of the sequence illustrated in SEQ ID24.

Example 8 - Preparation of a LC/A-nociceptin variant-H_N/A fusion protein

Following the methods used in Examples 1 and 2, the LC/A (SEQ ID1) and H_N/A (SEQ ID2) are created and inserted into the A serotype nociceptin variant linker arranged as *Bam*HI-*Sal*I-linker-protease site-nociceptin variant-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hin*dIII (SEQ ID12). The final construct contains the LC-linker-nociceptin variant-spacer-H_N ORF (SEQ ID25) for expression as a protein of the sequence illustrated in SEQ ID26.

Example 9 – Purification method for LC/A-nociceptin-H_N/A fusion protein

Defrost falcon tube containing 25 ml 50 mM HEPES pH 7.2, 200 mM NaCl and approximately 10 g of *E. coli* BL21 cell paste. Make the thawed cell paste up to 80 ml with 50 mM HEPES pH 7.2, 200 mM NaCl and sonicate on ice 30 seconds on, 30 seconds off for 10 cycles at a power of 22 microns ensuring the sample remains cool. Spin the lysed cells at 18 000 rpm, 4°C for 30 minutes. Load the supernatant onto a 0.1 M $NiSO_4$ charged Chelating column (20-30 ml column is

sufficient) equilibrated with 50 mM HEPES pH 7.2, 200 mM NaCl. Using a step gradient of 10 and 40 mM imidazol, wash away the non-specific bound protein and elute the fusion protein with 100 mM imidazol. Dialyse the eluted fusion protein against 5 L of 50 mM HEPES pH 7.2, 200 mM NaCl at 4°C overnight and measure the OD of the dialysed fusion protein. Add 1 unit of factor Xa per 100 µg fusion protein and Incubate at 25°C static overnight. Load onto a 0.1 M $NiSO_4$ charged Chelating column (20-30 ml column is sufficient) equilibrated with 50 mM HEPES pH 7.2, 200 mM NaCl. Wash column to baseline with 50 mM HEPES pH 7.2, 200 mM NaCl. Using a step gradient of 10 and 40 mM imidazol, wash away the non-specific bound protein and elute the fusion protein with 100 mM imidazol. Dialyse the eluted fusion protein against 5 L of 50 mM HEPES pH 7.2, 200 mM NaCl at 4°C overnight and concentrate the fusion to about 2 mg/ml, aliquot sample and freeze at -20°C. Test purified protein using OD, BCA, purity analysis and SNAP-25 assessments.

Example 10 – Confirmation of TM Agonist Activity by measuring release of substance P from neuronal cell cultures

Materials

Substance P EIA is obtained from R&D Systems, UK.

Methods

Primary neuronal cultures of eDRG are established as described previously (Duggan *et al.*, 2002). Substance P release from the cultures is assessed by EIA, essentially as described previously (Duggan *et al.*, 2002). The TM of interest is added to the neuronal cultures (established for at least 2 weeks prior to treatment); control cultures are performed in parallel by addition of vehicle in place of TM. Stimulated (100 mM KCl) and basal release, together with total cell lysate content, of substance P are obtained for both control and TM treated cultures. Substance P immunoreactivity is measured using Substance P Enzyme

Immunoassay Kits (Cayman Chemical Company, USA or R&D Systems, UK) according to manufacturers' instructions.

The amount of Substance P released by the neuronal cells in the presence of the TM of interest is compared to the release obtained in the presence and absence of 100 mM KCl. Stimulation of Substance P release by the TM of interest above the basal release, establishes that the TM of interest is an "agonist ligand" as defined in this specification. If desired the stimulation of Substance P release by the TM of interest can be compared to a standard Substance P release-curve produced using the natural ORL-1 receptor ligand, nociceptin (Tocris).

Example 11 - Confirmation of ORL_1 receptor activation by measuring forskolin-stimulated cAMP production

Confirmation that a given TM is acting via the ORL_1 receptor is provided by the following test, in which the TMs ability to inhibit forskolin-stimulated cAMP production is assessed.

Materials

[^{3}H]adenine and [^{14}C]cAMP are obtained from GE Healthcare

Methods

The test is conducted essentially as described previously by Meunier *et al.* [Isolation and structure of the endogenous agonist of opioid receptor-like ORL_1 receptor. Nature 377: 532-535, 1995] in intact transfected-CHO cells plated on 24-well plastic plates.

To the cells is added [3H]adenine (1.0 µCi) in 0.4 ml of culture medium. The cells remain at 37°C for 2 h to allow the adenine to incorporate into the intracellular ATP pool. After 2 h, the cells are washed once with incubation buffer containing: 130 mM NaCl, 4.8 mM KCl, 1.2 mM KH_2PO_4, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 10

mM glucose, 1 mg/ml bovine serum albumin and 25 mM HEPES pH 7.4, and replaced with buffer containing forskolin (10 μM) and isobutylmethylxanthine (50 μM) with or without the TM of interest. After 10 min, the medium is aspirated and replaced with 0.5 ml, 0.2 M HCl. Approximately 1000 cpm of [^{14}C]cAMP is added to each well and used as an internal standard. The contents of the wells are then transferred to columns of 0.65 g dry alumina powder. The columns are eluted with 4 ml of 5 mM HCl, 0.5 ml of 0.1 M ammonium acetate, then two additional millilitres of ammonium acetate. The final eluate is collected into scintillation vials and counted for ^{14}C and tritium. Amounts collected are corrected for recovery of [^{14}C]cAMP. TMs that are agonists at the ORL_1 receptor cause a reduction in the level of cAMP produced in response to forskolin.

Example 12 - Confirmation of ORL_1 receptor activation using a GTPγS binding functional assay

Confirmation that a given TM is acting via the ORL_1 receptor is also provided by the following test, a GTPγS binding functional assay.

Materials

[^{35}S]GTPγS is obtained from GE Healthcare

Wheatgerm agglutinin-coated (SPA) beads are obtained from GE Healthcare

Methods

This assay is carried out essentially as described by Traynor and Nahorski [Modulation by μ-opioid agonists of guanosine-5 -O-(3-[^{35}S]thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. Mol. Pharmacol. 47: 848-854, 1995].

Cells are scraped from tissue culture dishes into 20 mM HEPES, 1 mM ethylenediaminetetraacetic acid, then centrifuged at 500 × *g* for 10 min. Cells are resuspended in this buffer and homogenized with a Polytron Homogenizer.

The homogenate is centrifuged at 27,000 × *g* for 15 min, and the pellet resuspended in buffer A, containing: 20 mM HEPES, 10 mM $MgCl_2$, 100 mM NaCl, pH 7.4. The suspension is recentrifuged at 20,000 × *g* and suspended once more in buffer A. For the binding assay, membranes (8-15 µg protein) are incubated with [^{35}S]GTP S (50 pM), GDP (10 µM), with and without the TM of interest, in a total volume of 1.0 ml, for 60 min at 25°C. Samples are filtered over glass fibre filters and counted as described for the binding assays.

Example 13 – Preparation of a LC/A-nociceptin-H_N/A fusion protein (nociceptin is N-terminal of the H_N-chain)

The linker-nociceptin-spacer insert is prepared as described in Example 2.

Preparation of the LC/A-nociceptin-H_N/A fusion

In order to create the LC-linker-nociceptin-spacer-H_N construct (SEQ ID13), the pCR 4 vector encoding the linker (SEQ ID7) is cleaved with *Bam*HI + *Sal*I restriction enzymes. This cleaved vector then serves as the recipient for insertion and ligation of the LC/A DNA (SEQ ID1) also cleaved with *Bam*HI + *Sal*I. The resulting plasmid DNA is then cleaved with *Bam*HI + *Hind*III restriction enzymes and the LC/A-linker fragment inserted into a similarly cleaved vector containing a unique multiple cloning site for *Bam*HI, *Sal*I, *Pst*I, and *Hind*III such as the pMAL vector (NEB). The H_N/A DNA (SEQ ID2) is then cleaved with *Pst*I + *Hind*III restriction enzymes and inserted into the similarly cleaved pMAL-LC/A-linker construct. The final construct contains the LC-linker-nociceptin-spacer-H_N ORF (SEQ ID13) for expression as a protein of the sequence illustrated in SEQ ID14.

Example 14 – Preparation of a nociceptin-LC/A-H_N/A fusion protein (nociceptin is N-terminal of the LC-chain)

In order to create the nociceptin-spacer-LC/A-H_N/A construct, an A serotype linker with the addition of a Factor Xa site for activation, arranged as *Bam*HI-*Sal*I-

linker-protease site-linker-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID8) is synthesised as described in Example 13. The pCR 4 vector encoding the linker is cleaved with *Bam*HI + *Sal*I restriction enzymes. This cleaved vector then serves as the recipient for insertion and ligation of the LC/A DNA (SEQ ID1) also cleaved with *Bam*HI + *Sal*I. The resulting plasmid DNA is then cleaved with *Bam*HI + *Hind*III restriction enzymes and the LC/A-linker fragment inserted into a similarly cleaved vector containing the synthesised N-terminal presentation nociceptin insert (SEQ ID9). This construct is then cleaved with *Ava*I + *Hind*III and inserted into an expression vector such as the pMAL plasmid (NEB). The H_N/A DNA (SEQ ID2) is then cleaved with *Pst*I + *Hind*III restriction enzymes and inserted into the similarly cleaved pMAL-nociceptin-LC/A-linker construct. The final construct contains the nociceptin-spacer-LC/A-H_N/A ORF (SEQ ID51) for expression as a protein of the sequence illustrated in SEQ ID52.

Example 15 - Preparation and purification of an LC/A-nociceptin-H_N/A fusion protein family with variable spacer length

Using the same strategy as employed in Example 2, a range of DNA linkers were prepared that encoded nociceptin and variable spacer content. Using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)], the DNA sequence encoding the linker-ligand-spacer region is determined. Restriction sites are then incorporated into the DNA sequence and can be arranged as *Bam*HI-*Sal*I-linker-protease site-nociceptin-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hind*III (SEQ ID53 to SEQ ID57). It is important to ensure the correct reading frame is maintained for the spacer, nociceptin and restriction sequences and that the *Xba*I sequence is not preceded by the bases, TC which would result on DAM methylation. The DNA sequence is screened for restriction sequence incorporation and any additional sequences are removed manually from the remaining sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and

codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector.

The spacers that were created included:

Code	Protein sequence of the linker	SEQ ID of the linker DNA
GS10	ALAGGGGSALVLQ	53
GS15	ALAGGGGSGGGGSALVLQ	54
GS25	ALAGGGGSGGGGSGGGGSGGGGSALVLQ	55
GS30	ALAGGGGSGGGGSGGGGSGGGGSGGGGSALVLQ	56
HX27	ALAAEAAAKEAAAKEAAAKAGGGGSALVLQ	57

Table 1

By way of example, in order to create the LC/A-CPN(GS15)-H_N/A fusion construct (SEQ ID58), the pCR 4 vector encoding the linker (SEQ ID54) is cleaved with *Bam*HI + *Sal*I restriction enzymes. This cleaved vector then serves as the recipient vector for insertion and ligation of the LC/A DNA (SEQ ID1) also cleaved with *Bam*HI + *Sal*I. The resulting plasmid DNA is then cleaved with *Bam*HI + *Hind*III restriction enzymes and the LC/A-linker fragment inserted into a similarly cleaved vector containing a unique multiple cloning site for *Bam*HI, *Sal*I, *Pst*I, and *Hind*III such as the pMAL vector (NEB). The H_N/A DNA (SEQ ID2) is then cleaved with *Pst*I + *Hind*III restriction enzymes and inserted into the similarly cleaved pMAL-LC/A-linker construct. The final construct contains the LC/A-CPN(GS15)-H_N/A ORF (SEQ ID58) for expression as a protein of the sequence illustrated in SEQ ID59.

As a further example, to create the LC/A-CPN(GS25)-H_N/A fusion construct (SEQ ID60), the pCR 4 vector encoding the linker (SEQ ID55) is cleaved with *Bam*HI + *Sal*I restriction enzymes. This cleaved vector then serves as the recipient vector

for insertion and ligation of the LC/A DNA (SEQ ID1) cleaved with *Bam*HI + *Sal*I. The resulting plasmid DNA is then cleaved with *Bam*HI + *Hind*III restriction enzymes and the LC/A-linker fragment inserted into a similarly cleaved vector containing a unique multiple cloning site for *Bam*HI, *Sal*I, *Pst*I, and *Hind*III such as the pMAL vector (NEB). The H_N/A DNA (SEQ ID2) is then cleaved with *Pst*I + *Hind*III restriction enzymes and inserted into the similarly cleaved pMAL-LC/A-linker construct. The final construct contains the LC/A-CPN(GS25)-H_N/A ORF (SEQ ID60) for expression as a protein of the sequence illustrated in SEQ ID61.

Variants of the LC/A-CPN-H_N/A fusion consisting of GS10, GS30 and HX27 are similarly created. Using the purification methodology described in Example 9, fusion protein is purified from *E. coli* cell paste. Figure 9 illustrates the purified product obtained in the case of LC/A-CPN(GS10)-H_N/A, LC/A-CPN(GS15)-H_N/A, LC/A-CPN(GS25)-H_N/A, LC/A-CPN(GS30)-H_N/A and LC/A-CPN(HX27)-H_N/A.

Example 16 - Assessment of *in vitro* efficacy of an LC/A-nociceptin-H_N/A fusion

Fusion protein prepared according to Examples 2 and 9 was assessed in the eDRG neuronal cell model.

Assays for the inhibition of substance P release and cleavage of SNAP-25 have been previously reported (Duggan *et al.*, 2002, *J. Biol. Chem.*, 277, 34846-34852). Briefly, dorsal root ganglia neurons are harvested from 15-day-old fetal Sprague-Dawley rats and dissociated cells plated onto 24-well plates coated with Matrigel at a density of 1 x 10^6 cells/well. One day post-plating the cells are treated with 10 µM cytosine β-D-arabinofuranoside for 48 h. Cells are maintained in Dulbecco's minimal essential medium supplemented with 5% heat-inactivated fetal bovine serum, 5 mM L-glutamine, 0.6% D-glucose, 2% B27 supplement, and 100 ng/ml 2.5S mouse nerve growth factor. Cultures are maintained for 2 weeks at 37°C in 95% air/5% CO_2 before addition of test materials.

Release of substance P from eDRG is assessed by enzyme-linked immunosorbent assay. Briefly, eDRG cells are washed twice with low potassium-balanced salt solution (BSS: 5 mM KCl, 137 mM NaCl, 1.2 mM $MgCl_2$, 5 mM glucose, 0.44 mM KH_2PO_4, 20 mM HEPES, pH 7.4, 2 mM $CaCl_2$). Basal samples are obtained by incubating each well for 5 min. with 1 ml of low potassium BSS. After removal of this buffer, the cells are stimulated to release by incubation with 1 ml of high potassium buffer (BSS as above with modification to include 100 mM KCl isotonically balanced with NaCl) for 5 min. All samples are removed to tubes on ice prior to assay of substance P. Total cell lysates are prepared by addition of 250 µl of 2 M acetic acid/0.1% trifluoroacetic acid to lyse the cells, centrifugal evaporation, and resuspension in 500 µl of assay buffer. Diluted samples are assessed for substance P content. Substance P immunoreactivity is measured using Substance P Enzyme Immunoassay Kits (Cayman Chemical Company or R&D Systems) according to manufacturers' instructions. Substance P is expressed in pg/ml relative to a standard substance P curve run in parallel.

SDS-PAGE and Western blot analysis were performed using standard protocols (Novex). SNAP-25 proteins were resolved on a 12% Tris/glycine polyacrylamide gel (Novex) and subsequently transferred to nitrocellulose membrane. The membranes were probed with a monoclonal antibody (SMI-81) that recognises cleaved and intact SNAP-25. Specific binding was visualised using peroxidase-conjugated secondary antibodies and a chemiluminescent detection system. Cleavage of SNAP-25 was quantified by scanning densitometry (Molecular Dynamics Personal SI, ImageQuant data analysis software). Percent SNAP-25 cleavage was calculated according to the formula: (Cleaved SNAP-25/(Cleaved+Intact SNAP-25))x100.

Following exposure of eDRG neurons to an LC/A-nociceptin-H_N/A fusion (termed CPN-A), both inhibition of substance P release and cleavage of SNAP-25 are

observed (Figure 10). After 24 h exposure to the fusion, 50% of maximal SNAP-25 cleavage is achieved by a fusion concentration of 6.3±2.5 nM.

The effect of the fusion is also assessed at defined time points following a 16 h exposure of eDRG to CPN-A. Figure 11 illustrates the prolonged duration of action of the CPN-A fusion protein, with measurable activity still being observed at 28 days post exposure.

Example 17 - Assessment of *in vitro* efficacy of an LC/A-nociceptin variant-H_N/A fusion

Fusion protein prepared according to Examples 8 and 9 was assessed in the eDRG neuronal cell mode using the method described in Example 16.

Following exposure of eDRG neurons to an LC/A-nociceptin variant-H_N/A fusion (termed CPNv-A), both inhibition of substance P release and cleavage of SNAP-25 are observed. After 24 h exposure to the fusion, 50% of maximal SNAP-25 cleavage is achieved by a fusion concentration of 1.4±0.4 nM (Figure 12).

The effect of the fusion is also assessed at defined time points following a 16 h exposure of eDRG to CPN-A. Figure 13 illustrates the prolonged duration of action of the CPN-A fusion protein, with measurable activity still being observed at 24 days post exposure.

The binding capability of the CPNv-A fusion protein is also assessed in comparison to the CPN-A fusion. Figure 14 illustrates the results of a competition experiment to determine binding efficacy at the ORL-1 receptor. CPNv-A is demonstrated to displace [3H]-nociceptin, thereby confirming that access to the receptor is possible with the ligand in the central presentation format.

Example 18 - Preparation of an LC/A-nociceptin variant-H_N/A fusion protein that is activated by treatment with Enterokinase

Following the methods used in Examples 1 and 2, the LC/A (SEQ ID1) and H_N/A (SEQ ID2) are created and inserted into the A serotype nociceptin variant linker arranged as *Bam*HI-*Sal*I-linker-enterokinase protease site-nociceptin variant-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hin*dIII (SEQ ID62). The final construct contains the LC-linker-nociceptin variant-spacer-H_N ORF sequences (SEQ ID63) for expression as a protein of the sequence illustrated in SEQ ID64. The fusion protein is termed CPNv(Ek)-A. Figure 15 illustrates the purification of CPNv(Ek)-A from *E. coli* following the methods used in Example 9 but using Enterokinase for activation at 0.00064 µg per 100 µg of fusion protein.

Example 19 - Assessment of *in vitro* efficacy of a LC/A-nociceptin variant-H_N/A fusion that has been activated by treatment with enterokinase

The CPNv(Ek)-A prepared in Example 18 is obtained in a purified form and applied to the eDRG cell model to assess cleavage of SNAP-25 (using methodology from Example 16). Figure 16 illustrates the cleavage of SNAP-25 following 24 h exposure of eDRG to CPNv(Ek)-A. The efficiency of cleavage is observed to be similar to that achieved with the Factor Xa-cleaved material, as recorded in Example 17.

Example 20 - Preparation of an LC/C-nociceptin variant-H_N/C fusion protein with a Factor Xa activation linker derived from serotype A

Following the methods used in Example 4, the LC/C (SEQ ID5) and H_N/C (SEQ ID6) are created and inserted into the A serotype nociceptin variant linker arranged as *Bam*HI-*Sal*I-linker-nociceptin variant-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hin*dIII (SEQ ID65). The final construct contains the LC-linker-nociceptin variant-spacer-H_N ORF sequences (SEQ ID66) for expression as a protein of the sequence illustrated in SEQ ID67. The fusion protein is termed

CPNv-C (act. A). Figure 17 illustrates the purification of CPNv-C (act. A) from *E. coli* following the methods used in Example 9.

Example 21 - Assessment of *in vitro* efficacy of an LC/C-nociceptin variant-H_N/C fusion protein

Following the methods used in Example 9, the CPNv-C (act. A) prepared in Example 20 is obtained in a purified form and applied to the eDRG cell model to assess cleavage of SNAP-25 (using methodology from Example 16). After 24 h exposure to the fusion, 50% of maximal syntaxin cleavage is achieved by a fusion concentration of 3.1±2.0 nM. Figure 18 illustrates the cleavage of syntaxin following 24 h exposure of eDRG to CPNv-C (act. A).

Example 22 - Assessment of *in vivo* efficacy of an LC/A-nociceptin-HN/A fusion

The ability of an LC/A-nociceptin- H_N/A fusion (CPN/A) to inhibit acute capsaicin-induced mechanical allodynia is evaluated following subcutaneous intraplantar injection in the rat hind paw. Test animals are evaluated for paw withdrawal frequency (PWF%) in response to a 10 g Von Frey filament stimulus series (10 stimuli x 3 trials) prior to recruitment into the study, after subcutaneous treatment with CPN/A but before capsaicin, and following capsaicin challenge post-injection of CPN/A (average of responses at 15' and 30'). Capsaicin challenge is achieved by injection of 10 µL of a 0.3% solution. Sample dilutions are prepared in 0.5% BSA/saline. Figure 19 illustrates the reversal of mechanical allodynia that is achieved by pre-treatment of the animals with a range of concentrations of LC/A-nociceptin-HN/A fusion.

The ability of an LC/A-nociceptin-HN/A fusion (CPN/A) to inhibit streptozotocin (STZ)– induced mechanical (tactile) allodynia in rats is evaluated. STZ–induced mechanical allodynia in rats is achieved by injection of streptozotocin (i.p. or i.v.) which yields destruction of pancreatic β-cells leading to loss of insulin production,

with concomitant metabolic stress (hyperglycemia and hyperlipidemia). As such, STZ induces Type I diabetes. In addition, STZ treatment leads to progressive development of neuropathy, which serves as a model of chronic pain with hyperalgesia and allodynia that may reflect signs observed in diabetic humans (peripheral diabetic neuropathy).

Male Sprague-Dawley rats (250-300 g) are treated with 65 mg/kg STZ in citrate buffer (I.V.) and blood glucose and lipid are measured weekly to define the readiness of the model. Paw Withdrawal Threshold (PWT) is measured in response to a Von Frey filament stimulus series over a period of time. Allodynia is said to be established when the PWT on two consecutive test dates (separated by 1 week) measures below 6 g on the scale. At this point, rats are randomized to either a saline group (negative efficacy control), gabapentin group (positive efficacy control) or a test group (CPN/A). Test materials (20-25 µl) are injected subcutaneously as a single injection (except gabapentin) and the PWT is measured at 1 day post-treatment and periodically thereafter over a 2-week period. Gabapentin (30 mg/kg i.p. @ 3 ml/kg injection volume) is injected daily, 2 hours prior to the start of PWT testing. Figure 20 illustrates the reversal of allodynia achieved by pre-treatment of the animals with 750 ng of CPN/A. Data were obtained over a 2-week period after a single injection of CPN/A

Example 23 - Assessment of *in vivo* efficacy of an LC/A-nociceptin variant-H_N/A fusion

The ability of an LC/A-nociceptin variant-H_N/A fusion (CPNv/A) to inhibit capsaicin-induced mechanical allodynia is evaluated following subcutaneous intraplantar injection in the rat hind paw. Test animals are evaluated for paw withdrawal frequency (PWF%) in response to a 10 g Von Frey filament stimulus series (10 stimuli x 3 trials) prior to recruitment into the study (Pre-Treat); after subcutaneous intraplantar treatment with CPNv/A but before capsaicin (Pre-CAP); and following capsaicin challenge post-injection of CPNv/A (average of

responses at 15' and 30'; CAP). Capsaicin challenge is achieved by injection of 10 µL of a 0.3% solution. Sample dilutions are prepared in 0.5% BSA/saline.

Figure 21 illustrates the reversal of allodynia that is achieved by pre-treatment of the animals with a range of concentrations of LC/A-nociceptin variant-H_N/A fusion in comparison to the reversal achieved with the addition of LC/A-nociceptin-H_N/A fusion. These data are expressed as a normalized paw withdrawal frequency differential, in which the difference between the peak response (post-capsaicin) and the baseline response (pre-capsaicin) is expressed as a percentage. With this analysis, it can be seen that CPNv/A is more potent than CPN/A since a lower dose of CPNv/A is required to achieve similar analgesic effect to that seen with CPN/A.

Example 24 - Preparation of an LC/A-leu enkephalin-H_N/A fusion protein

Due to the small, five-amino acid, size of the leu-enkephalin ligand the LC/A-leu enkephalin-H_N/A fusion is created by site directed mutagenesis [for example using Quickchange (Stratagene Inc.)] using the LC/A-nociceptin-H_N/A fusion (SEQ ID13) as a template. Oligonucleotides are designed encoding the YGGFL leu-enkephalin peptide, ensuring standard *E. coli* codon usage is maintained and no additional restriction sites are incorporated, flanked by sequences complimentary to the linker region of the LC/A-nociceptin-H_N/A fusion (SEQ ID13) either side on the nociceptin section. The SDM product is checked by sequencing and the final construct containing the LC-linker-leu enkephalin-spacer-H_N ORF (SEQ ID68) for expression as a protein of the sequence illustrated in SEQ ID69. The fusion protein is termed CPLE-A. Figure 22 illustrates the purification of CPLE-A from *E. coli* following the methods used in Example 9.

Example 25 – Expression and purification of an LC/A-beta-endorphin-H_N/A fusion protein

Following the methods used in Example 9, and with the LC/A-beta-endorphin-H_N/A fusion protein (termed CPBE-A) created in Example 7, the CPBE-A is purified from *E. coli*. Figure 23 illustrates the purified protein as analysed by SDS-PAGE.

Example 26 - Preparation of an LC/A-nociceptin mutant-H_N/A fusion protein

Due to the single amino acid modification necessary to mutate the nociceptin sequence at position 1 from a Phe to a Tyr, the LC/A-nociceptin mutant-H_N/A fusion is created by site directed mutagenesis [for example using Quickchange (Stratagene Inc.)] using the LC/A-nociceptin-H_N/A fusion (SEQ ID13) as a template. Oligonucleotides are designed encoding tyrosine at position 1 of the nociceptin sequence, ensuring standard *E. coli* codon usage is maintained and no additional restriction sites are incorporated, flanked by sequences complimentary to the linker region of the LC/A-nociceptin-H_N/A fusion (SEQ ID13) either side on the nociceptin section. The SDM product is checked by sequencing and the final construct containing the LC/A-nociceptin mutant-spacer-H_N/A fusion ORF (SEQ ID70) for expression as a protein of the sequence illustrated in SEQ ID71. The fusion protein is termed CPOP-A. Figure 24 illustrates the purification of CPOP-A from *E. coli* following the methods used in Example 9.

Example 27 - Preparation and assessment of an LC/A-nociceptin variant mutant-H_N/A fusion protein

Due to the single amino acid modification necessary to mutate the nociceptin sequence at position 1 from a Phe to a Tyr, the LC/A-nociceptin variant mutant-H_N/A fusion is created by site directed mutagenesis [for example using Quickchange (Stratagene Inc.)] using the LC/A-nociceptin variant-H_N/A fusion

(SEQ ID25) as a template. Oligonucleotides are designed encoding tyrosine at position 1 of the nociceptin sequence, ensuring standard *E. coli* codon usage is maintained and no additional restriction sites are incorporated, flanked by sequences complimentary to the linker region of the LC/A-nociceptin variant-H_N/A fusion (SEQ ID25) either side on the nociceptin section. The SDM product is checked by sequencing and the final construct containing the LC/A-nociceptin mutant-spacer-H_N/A fusion ORF (SEQ ID72) for expression as a protein of the sequence illustrated in SEQ ID73. The fusion protein is termed CPOPv-A. Figure 25 illustrates the purification of CPOPv-A from *E. coli* following the methods used in Example 9.

Using methodology described in Example 16, CPOPv-A is assessed for its ability to cleave SNAP-25 in the eDRG cell model. Figure 26 illustrates that CPOPv-A is able to cleave SNAP-25 in the eDRG model, achieving cleavage of 50% of the maximal SNAP-25 after exposure of the cells to approximately 5.9 nM fusion for 24 h.

Example 28 - Preparation of an IgA protease-nociceptin variant-H_N/A fusion protein

The IgA protease amino acid sequence was obtained from freely available database sources such as GenBank (accession number P09790). Information regarding the structure of the *N. Gonorrhoeae* IgA protease gene is available in the literature (Pohlner *et al.*, Gene structure and extracellular secretion of *Neisseria gonorrhoeae* IgA protease, *Nature*, 1987, 325(6103), 458-62). Using Backtranslation tool v2.0 (Entelechon), the DNA sequence encoding the IgA protease modified for *E. coli* expression was determined. A *Bam*HI recognition sequence was incorporated at the 5' end and a codon encoding a cysteine amino acid and *Sal*I recognition sequence were incorporated at the 3' end of the IgA DNA. The DNA sequence was screened using MapDraw, (DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that are found to be common to those required for

cloning were removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage was assessed Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables. This optimised DNA sequence (SEQ ID74) containing the IgA open reading frame (ORF) is then commercially synthesized.

The IgA (SEQ ID74) is inserted into the LC-linker-nociceptin variant-spacer-H_N ORF (SEQ ID25) using *Bam*HI and *Sal*I restriction enzymes to replace the LC with the IgA protease DNA. The final construct contains the IgA-linker-nociceptin variant-spacer-H_N ORF (SEQ ID75) for expression as a protein of the sequence illustrated in SEQ ID76.

Example 29 - Preparation and assessment of a nociceptin targeted endopeptidase fusion protein with a removable histidine purification tag.

DNA was prepared that encoded a Factor Xa removable his-tag (his6), although it is clear that alternative proteases site such as Enterokinase and alternative purification tags such as longer histidine tags are also possible. Using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)], the DNA sequence encoding the Factor Xa removable his-tag region is determined. Restriction sites are then incorporated into the DNA sequence and can be arranged as *Nhe*I-linker-*Spe*I-*Pst*I-H_N/A-*Xba*I-LEIEGRSGHHHHHHStop *codon-Hind*III (SEQ ID77). The DNA sequence is screened for restriction sequence incorporated and any additional sequences are removed manually from the remaining sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence is then commercially synthesized (for example by Entelechon, Geneart

or Sigma-Genosys) and is provided in the pCR 4 vector. In order to create CPNv-A-FXa-HT (SEQ ID78, removable his-tag construct) the pCR 4 vector encoding the removable his-tag is cleaved with *Nhe*I and *Hind*III. The *Nhe*I - *Hind*III fragment is then inserted into the LC/A-CPNv-H_N/A vector (SEQ ID25) that has also been cleaved by *Nhe*I and *Hind*III. The final construct contains the LC/A-linker-nociceptin variant-spacer-H_N-FXa-Histag-*Hind*III ORF sequences (SEQ ID78) for expression as a protein of the sequence illustrated in SEQ ID79. Figure 27 illustrates the purification of CPNv-A-FXa-HT from *E. coli* following the methods used in Example 9.

Example 30 - Preparation of a leu-enkephalin targeted endopeptidase fusion protein containing a translocation domain derived from diphtheria toxin

The DNA sequence is designed by back translation of the amino acid sequence of the translocation domain of the diphtheria toxin (obtained from freely available database sources such as GenBank (accession number 1XDTT) using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)]. Restriction sites are then incorporated into the DNA sequence and can be arranged as *Nhe*I-Linker-*Spe*I-*Pst*I- diphtheria translocation domain-*Xba*I-stop codon-*Hind*III (SEQ ID80). *PstI*/*Xba*I recognition sequences are incorporated at the 5' and 3' ends of the translocation domain respectively of the sequence maintaining the correct reading frame. The DNA sequence is screened (using software such as MapDraw, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that are found to be common to those required by the cloning system are removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence containing the diphtheria translocation domain is then

commercially synthesized as *Nhe*I-Linker-*Spe*I-*Pst*I- diphtheria translocation domain-*Xba*I-stop codon-*Hind*III (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector (Invitrogen). The pCR 4 vector encoding the diphtheria translocation domain is cleaved with *Nhe*I and *Xba*I. The *Nhe*I – *Xba*I fragment is then inserted into the LC/A-CPLE-H_N/A vector (SEQ ID68) that has also been cleaved by *Nhe*I and *Xba*I. The final construct contains the LC/A-leu-enkephalin-spacer-diphtheria translocation domain ORF sequences (SEQ ID81) for expression as a protein of the sequence illustrated in SEQ ID82.

Example 31 - Preparation of a nociceptin variant targeted endopeptidase fusion protein containing a LC domain derived from tetanus toxin.

The DNA sequence is designed by back translation of the tetanus toxin LC amino acid sequence (obtained from freely available database sources such as GenBank (accession number X04436) using one of a variety of reverse translation software tools [for example EditSeq best *E. coli* reverse translation (DNASTAR Inc.), or Backtranslation tool v2.0 (Entelechon)]. *Bam*HI/*Sal*I recognition sequences are incorporated at the 5' and 3' ends respectively of the sequence maintaining the correct reading frame (SEQ ID83). The DNA sequence is screened (using software such as MapDraw, DNASTAR Inc.) for restriction enzyme cleavage sequences incorporated during the back translation. Any cleavage sequences that are found to be common to those required by the cloning system are removed manually from the proposed coding sequence ensuring common *E. coli* codon usage is maintained. *E. coli* codon usage is assessed by reference to software programs such as Graphical Codon Usage Analyser (Geneart), and the %GC content and codon usage ratio assessed by reference to published codon usage tables (for example GenBank Release 143, 13 September 2004). This optimised DNA sequence containing the tetanus toxin LC open reading frame (ORF) is then commercially synthesized (for example by Entelechon, Geneart or Sigma-Genosys) and is provided in the pCR 4 vector (invitrogen). The pCR 4 vector encoding the TeNT LC is cleaved with B*am*HI and *Sal*I. The *Bam*HI – *Sal*I fragment is then inserted into the LC/A-CPNv-H_N/A

vector (SEQ ID25) that has also been cleaved by *Bam*HI and *Sal*I. The final construct contains the TeNT LC-linker-nociceptin variant-spacer-H_N ORF sequences (SEQ ID84) for expression as a protein of the sequence illustrated in SEQ ID85.

Example 32 - Preparation of an LC/C-nociceptin variant-H_N/C fusion protein with a native serotype C linker that is susceptible to Factor Xa cleavage

Following the methods used in Example 4, the LC/C (SEQ ID5) and H_N/C (SEQ ID6) are created and inserted into the C serotype nociceptin variant linker arranged as *Bam*HI-*Sal*I-linker-nociceptin variant-*Nhe*I-spacer-*Spe*I-*Pst*I-*Xba*I-stop codon-*Hin*dIII (SEQ ID86). The final construct contains the LC-linker-nociceptin variant-spacer-H_N ORF sequences (SEQ ID87) for expression as a protein of the sequence illustrated in SEQ ID88. The fusion protein is termed CPNv-C (act. C).

Claims:

1. A single chain, polypeptide fusion protein, comprising:
   a. a non-cytotoxic protease, or a fragment thereof, which protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of a nociceptive sensory afferent;
   b. a Targeting Moiety that is capable of binding to a Binding Site on the nociceptive sensory afferent, which Binding Site is capable of undergoing endocytosis to be incorporated into an endosome within the nociceptive sensory afferent;
   c. a protease cleavage site at which site the fusion protein is cleavable by a protease, wherein the protease cleavage site is located between the non-cytotoxic protease or fragment thereof and the Targeting Moiety; and
   d. a translocation domain that is capable of translocating the protease or protease fragment from within an endosome, across the endosomal membrane and into the cytosol of the nociceptive sensory afferent.

2. The fusion protein according to Claim 1, wherein the Targeting Moiety and the protease cleavage site are separated by at most 10 amino acid residues, preferably by at most 5 amino acid residues, and more preferably by at most zero amino acid residues.

3. The fusion protein according to Claim 1 or Claim 2, wherein the Targeting Moiety is located between the protease cleavage site and the translocation domain.

4. The fusion protein according to any preceding claim, wherein the non-cytotoxic protease is a clostridial neurotoxin L-chain or an IgA protease.

5. The fusion protein according to any preceding claim, wherein the translocation domain is the H_N domain of a clostridial neurotoxin.

6. The fusion protein according to any preceding claim, wherein the Targeting Moiety comprises at most 50 amino acid residues, preferably at most 40 amino acid residues, more preferably at least 30 amino acid residues, and most preferably at most 20 amino acid residues.

7. The fusion protein according to any of Claims 1-6, wherein the Targeting Moiety is an opioid.

8. The fusion protein according to any of Claim 1-6, wherein the Targeting Moiety is an agonist of a receptor present on a nociceptive sensory afferent.

9. The fusion protein according to Claim 8, wherein the Targeting Moiety is an agonist of a receptor present on a primary nociceptive sensory afferent.

10. The fusion protein according to any of Claims 1-6, wherein the Targeting Moiety binds to the ORL_1 receptor.

11. The fusion protein according to Claim 10, wherein the Targeting Moiety binds specifically to the ORL_1 receptor.

12. The fusion protein according to Claim 10 or 11, wherein the Targeting Moiety is an agonist of the ORL_1 receptor.

13. The fusion protein according to any one of Claims 10-12, wherein the Targeting Moiety has at least 70% homology to SEQ ID No. 38 or a fragment thereof.

14. The fusion protein according to Claim 13, wherein the Targeting Moiety as at least 80% homology to SEQ ID No. 38 or a fragment thereof.

15. The fusion protein according to Claim 14, wherein the Targeting Moiety has at least 90% homology to SEQ ID No. 38 or a fragment thereof.

16. The fusion protein according to Claim 15, wherein the Targeting Moiety has at least 95% homology to SEQ ID No. 38 or a fragment thereof.

17. The fusion protein according to any one of Claims 10-12, wherein the Targeting Moiety is SEQ ID No. 38 or a fragment thereof.

18. The fusion protein according to any of Claims 10-12, wherein the Targeting Moiety is one of SEQ ID Nos: 40, 42, 44, 46, 48 or 50.

19. The fusion protein according to any one of Claims 10-12, wherein the Targeting Moiety is nociceptin.

20. The fusion protein according to any of Claims 1-6, wherein the Targeting Moiety is selected from the group consisting of nociceptin, β-endorphin, endomorphine-1, endomorphine-2, dynorphin, met-enkephalin, leu-enkephalin, galanin, and PAR-2 peptide.

21. The fusion protein according to any preceding claim, wherein the fusion protein comprises a purification tag.

22. The fusion protein according to Claim 21, wherein the fusion protein comprises a purification tag, which is present at the N-terminal and/ or C-terminal end of the fusion protein.

23. The fusion protein according to Claim 21 or 22, wherein the purification tag is joined to the fusion protein by a peptide spacer molecule.

24. The fusion protein according to any preceding claim, wherein the translocation domain is separated from the Targeting Moiety by a peptide spacer molecule.

25. A polypeptide fusion protein comprising any one of SEQ ID NOs: 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 52, 59, 61, 64, 67, 69, 71, 73, 76, 79, 82, 85, or 88.

26. A nucleic acid sequence encoding the polypeptide fusion protein according to any preceding Claim.

27. A nucleic acid sequence according to Claim 26, wherein the nucleic acid molecule comprises any one of SEQ ID NOs: 1-13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 58, 60, 63, 66, 68, 70, 72, 75, 78, 81, 84, or 87.

28. A DNA vector, which comprises a promoter, a nucleic acid sequence according to Claim 26 or Claim 27, wherein said DNA sequence is located downstream of the promoter, and a terminator is located downstream of the DNA construct.

29. The complementary DNA strand of the DNA sequence according to Claim 26 or Claim 27.

30. A method for preparing a single-chain polypeptide fusion protein according to any of Claims 1-24, comprising expressing a nucleic acid sequence according to Claim 26 or Claim 27, or a DNA vector according to Claim 28, in a host cell.

31. A method of preparing a non-cytotoxic agent, comprising:

a. contacting a single-chain polypeptide fusion protein according to any of Claims 1-24 with a protease capable of cleaving the protease cleavage site;

b. cleaving the protease cleavage site; and thereby forming a di-chain fusion protein.

32. A non-cytotoxic polypeptide, obtainable by the method of Claim 31, wherein the polypeptide is a di-chain polypeptide, and wherein:

a. the first chain comprises the non-cytotoxic protease, or a fragment thereof, which protease or protease fragment is capable of cleaving a protein of the exocytic fusion apparatus of a nociceptive sensory afferent;

b. the second chain comprises the TM and the translocation domain that is capable of translocating the protease or protease fragment from within an endosome, across the endosomal membrane and into the cytosol of the nociceptive sensory afferent; and

the first and second chains are disulphide linked together.

33. Use of a fusion protein according to any of Claims 1-24 or a polypeptide according to Claim 32, for the manufacture of a medicament for treating, preventing or ameliorating pain.

34. Use according to Claim 33, wherein the pain is chronic pain.

35. A method of treating, preventing or ameliorating pain in a subject, comprising administering to said patient a therapeutically effective amount of a fusion protein according to any of Claims 1-24 or a polypeptide according to Claim 32.

36. A method according to Claim 35, wherein the pain is chronic pain.

Figure 1

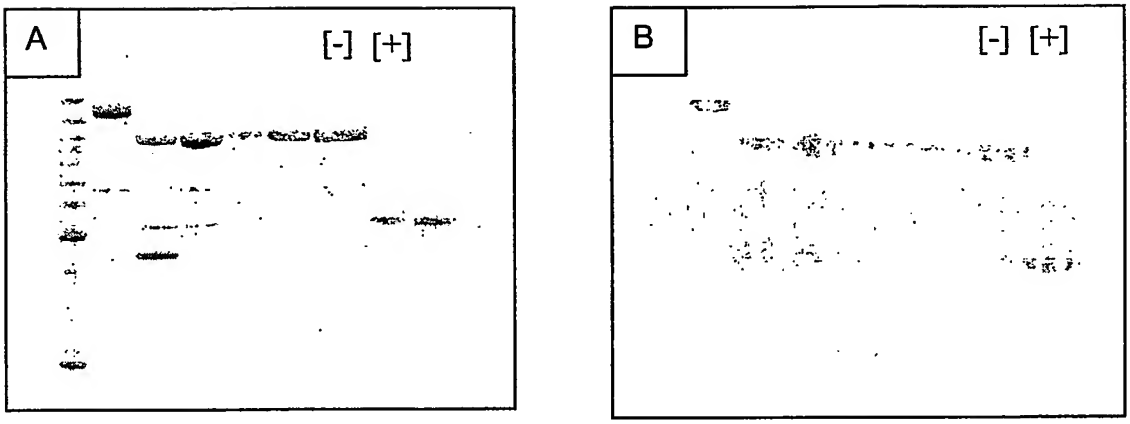


Figure 2

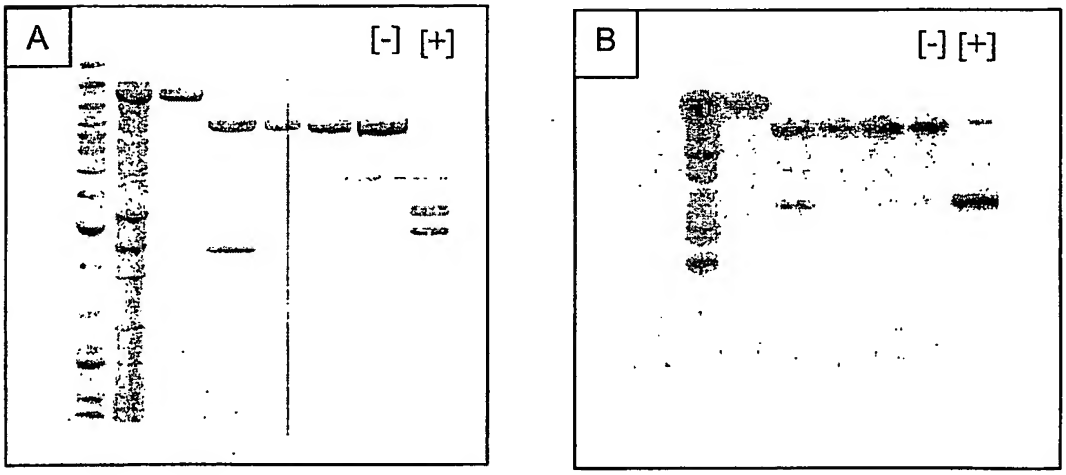


Figure 3

Figure 4

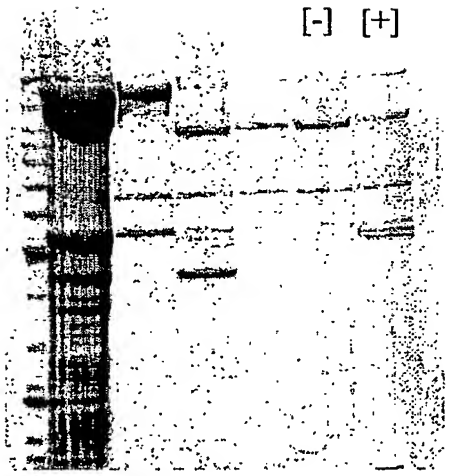


Figure 5

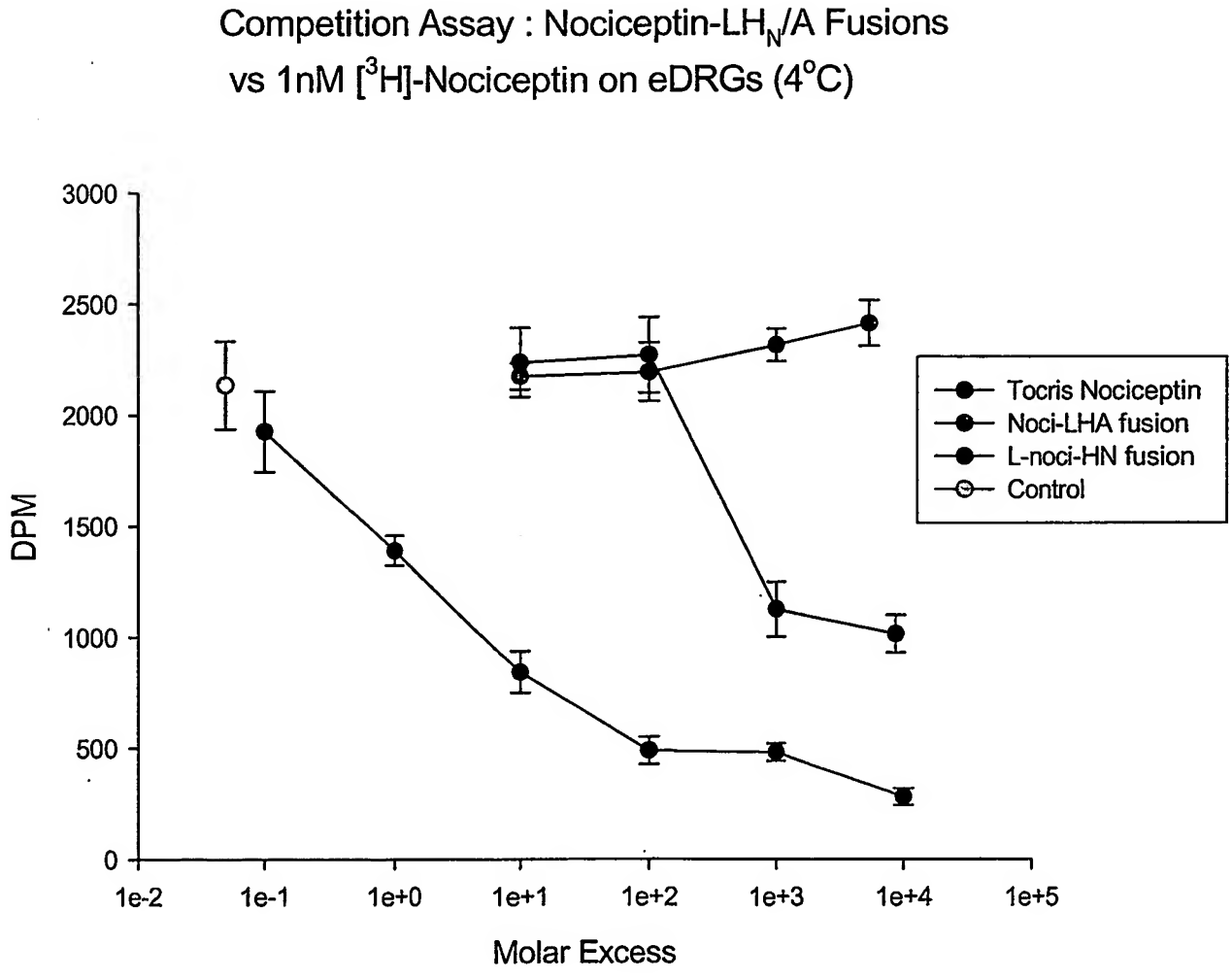

Competition Assay : Nociceptin-LH$_N$/A Fusions
vs 1nM [^{3}H]-Nociceptin on eDRGs (4°C)
DPM
3000
2500
2000
1500
1000
500
0
1e-2
1e-1
1e+0
1e+1
1e+2
1e+3
1e+4
1e+5
Molar Excess
Tocris Nociceptin
Noci-LHA fusion
L-noci-HN fusion
Control

Figure 6

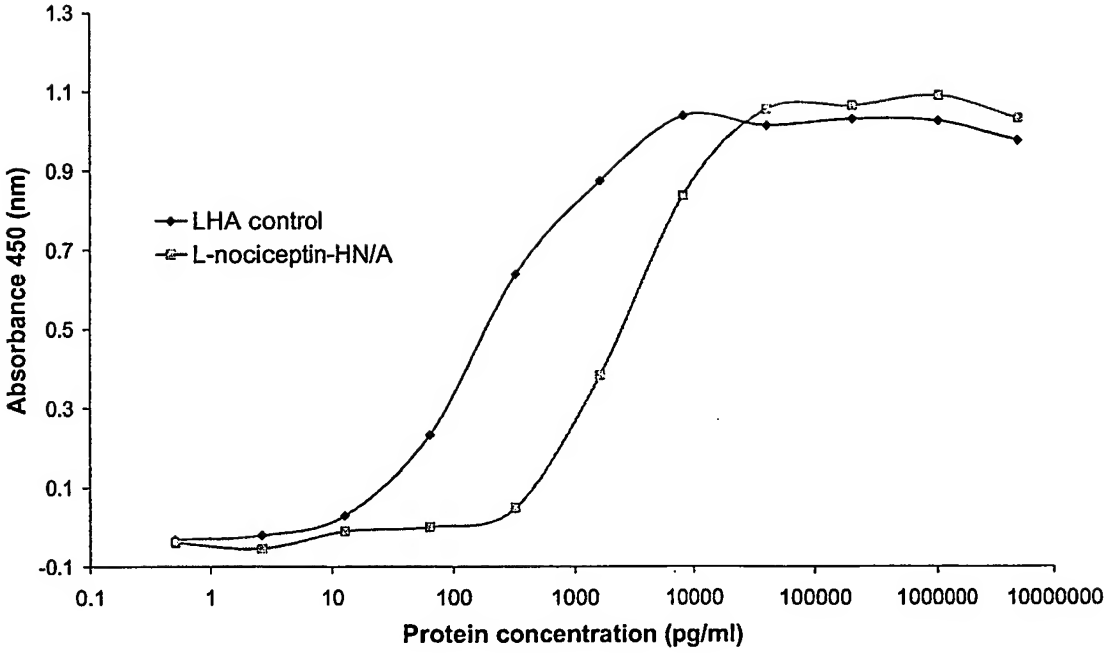

1.3
1.1
0.9
0.7
0.5
0.3
0.1
-0.1
Absorbance 450 (nm)
LHA control
L-nociceptin-HN/A
0.1
1
10
100
1000
10000
100000
1000000
10000000
Protein concentration (pg/ml)

Figure 7

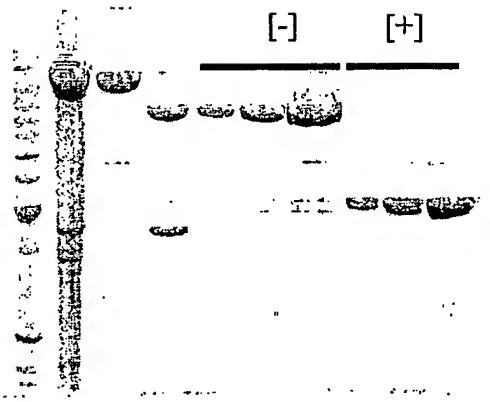


Figure 8

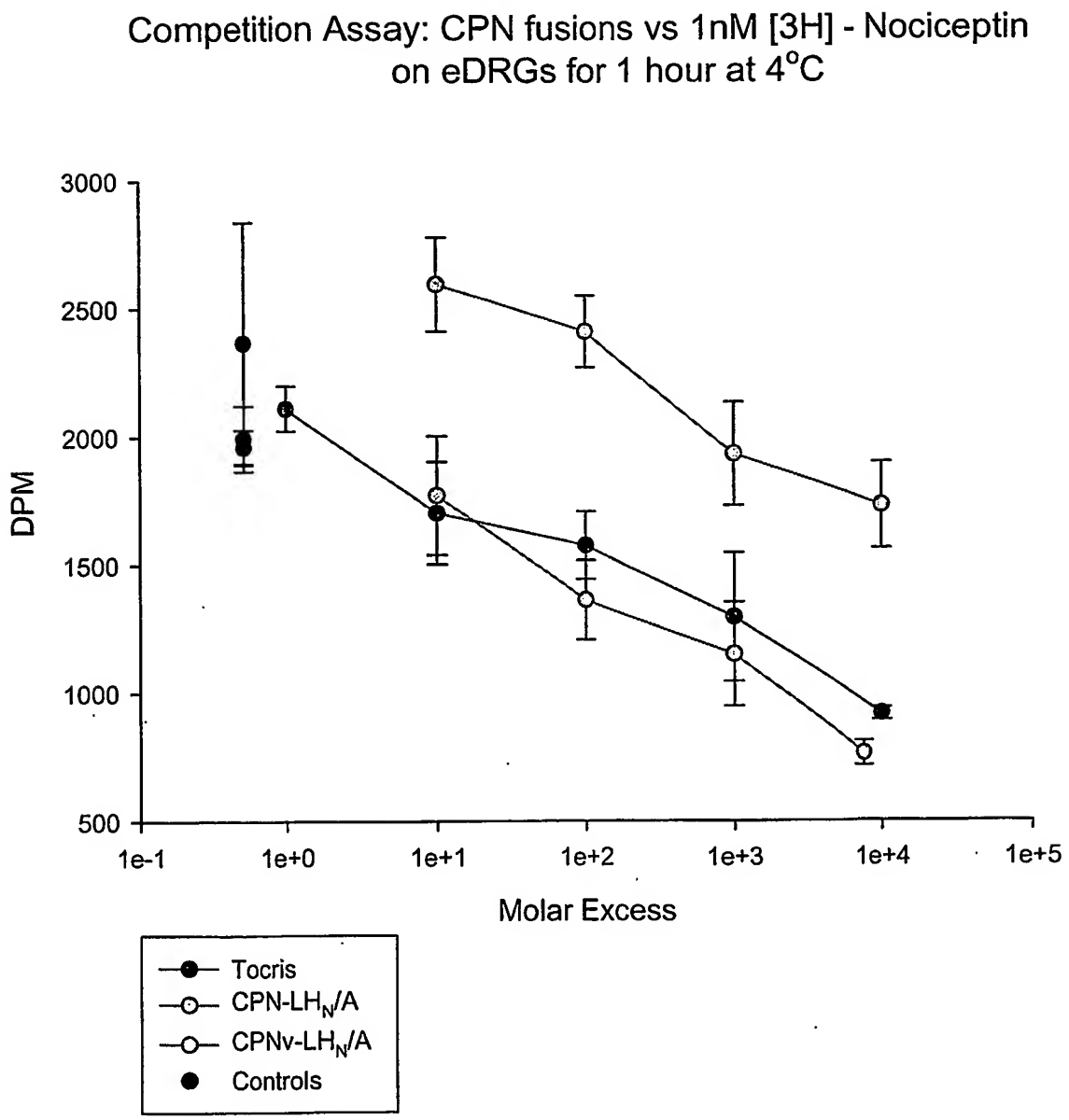

Competition Assay: CPN fusions vs 1nM [3H] - Nociceptin on eDRGs for 1 hour at 4°C
DPM
3000
2500
2000
1500
1000
500
1e-1
1e+0
1e+1
1e+2
1e+3
1e+4
1e+5
Molar Excess
Tocris
CPN-LH$_N$/A
CPNv-LH$_N$/A
Controls

Figure 9

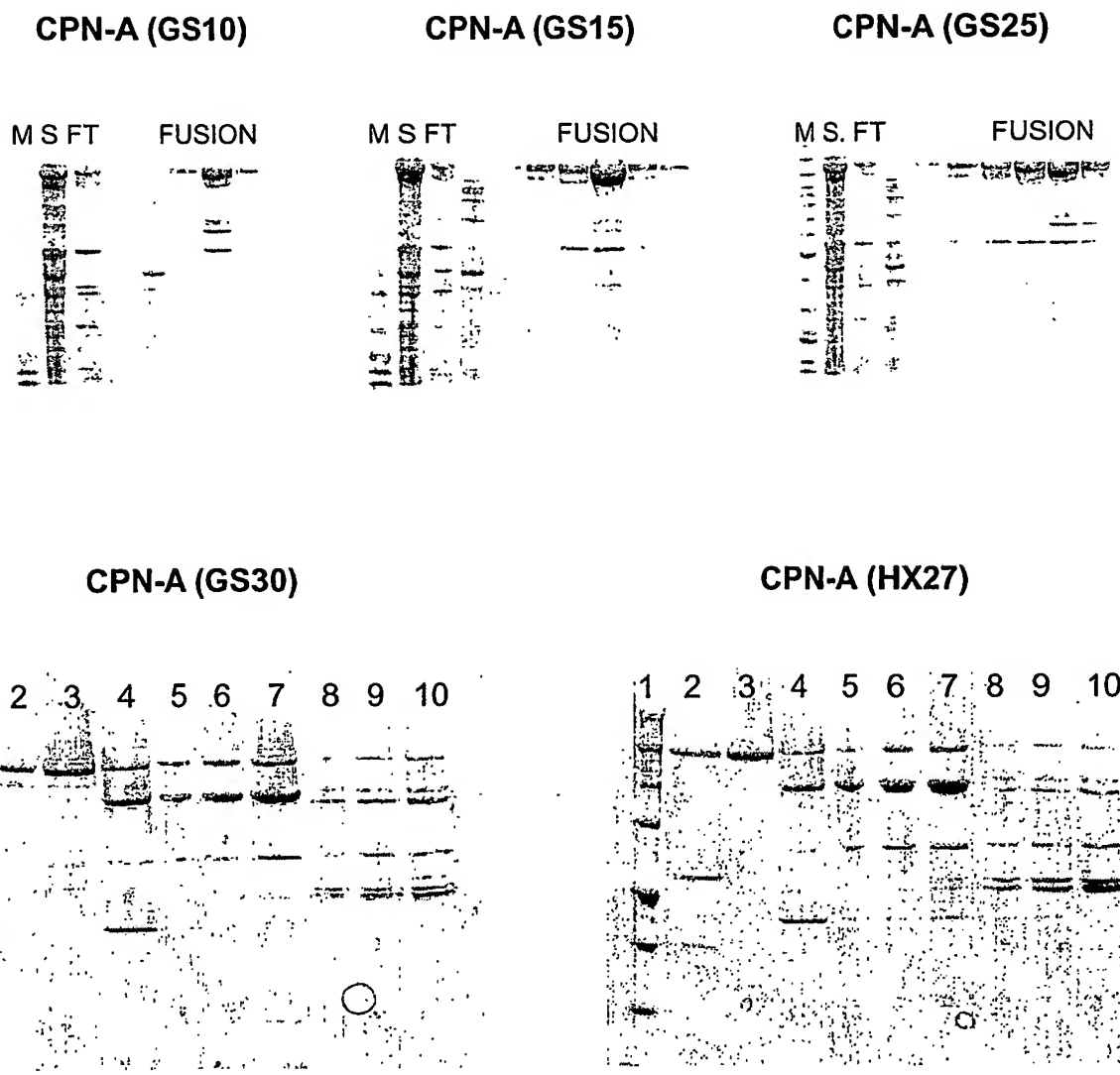

CPN-A (GS10)
M S FT
FUSION
CPN-A (GS15)
M S FT
FUSION
CPN-A (GS25)
M S. FT
FUSION
CPN-A (GS30)
1 2 3 4 5 6 7 8 9 10
CPN-A (HX27)
1 2 3 4 5 6 7 8 9 10

Figure 10

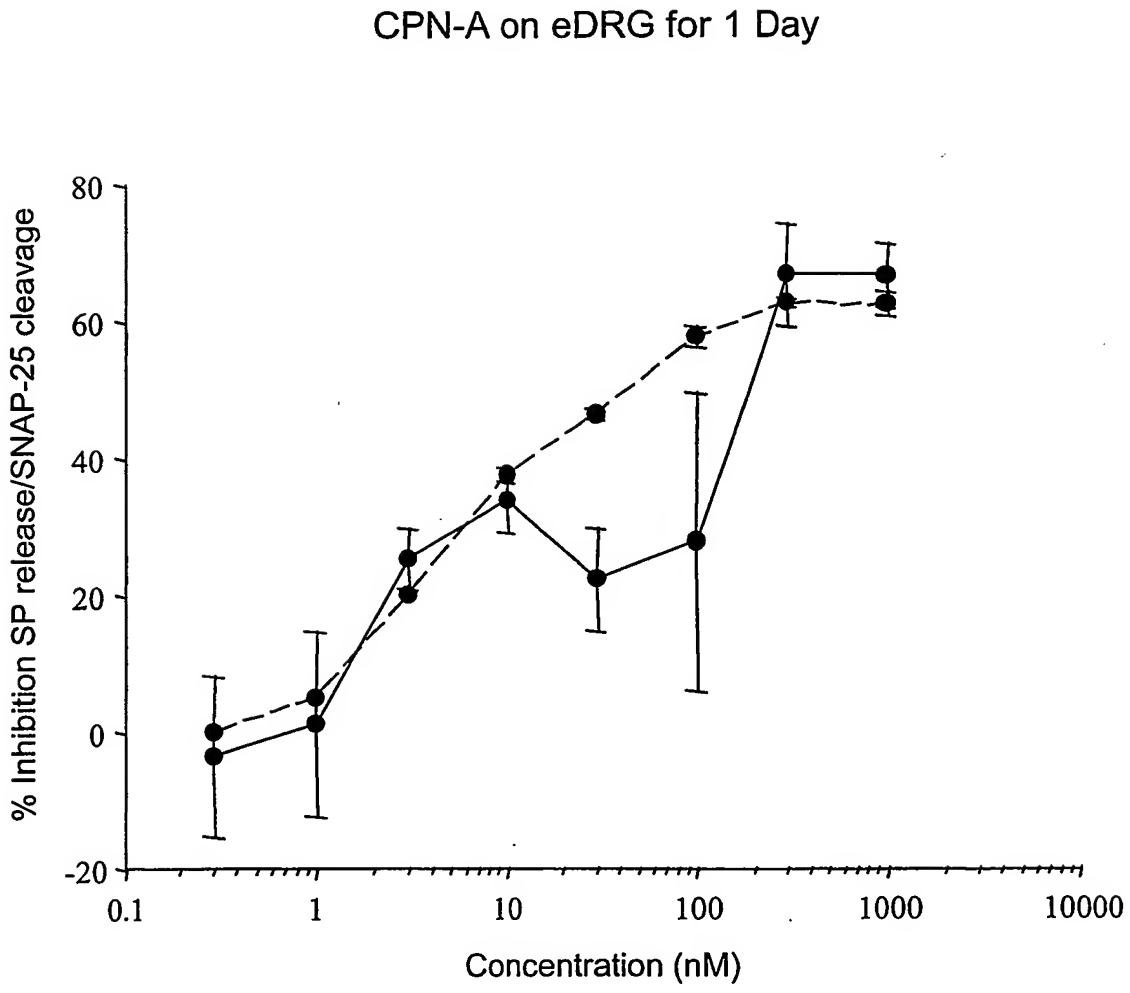

CPN-A on eDRG for 1 Day
% Inhibition SP release/SNAP-25 cleavage
80
60
40
20
0
-20
0.1
1
10
100
1000
10000
Concentration (nM)

Figure 11

Duration of action following eDRG exposure for 1 Day

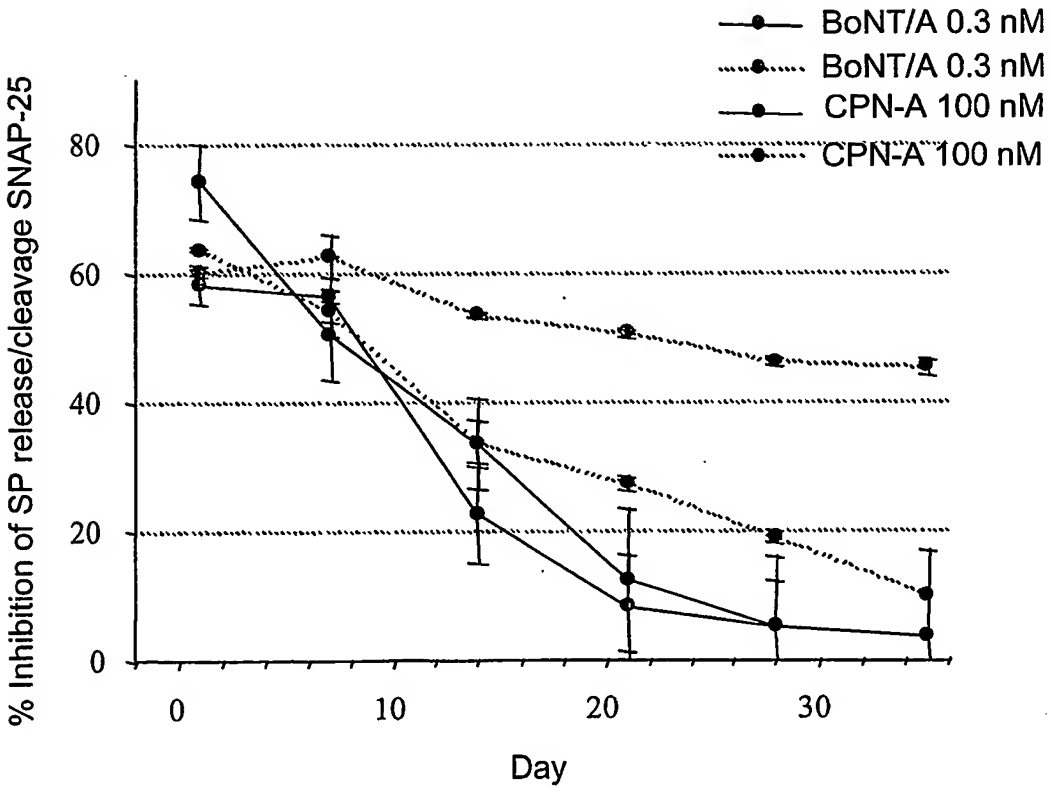


Figure 12

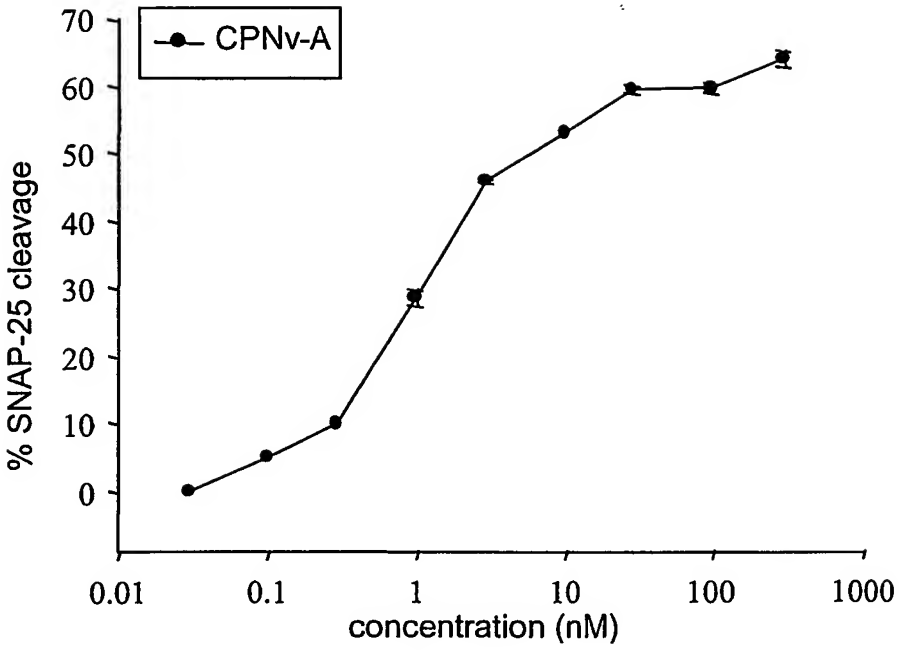

CPNv-A
% SNAP-25 cleavage
70
60
50
40
30
20
10
0
0.01
0.1
1
10
100
1000
concentration (nM)

Figure 13

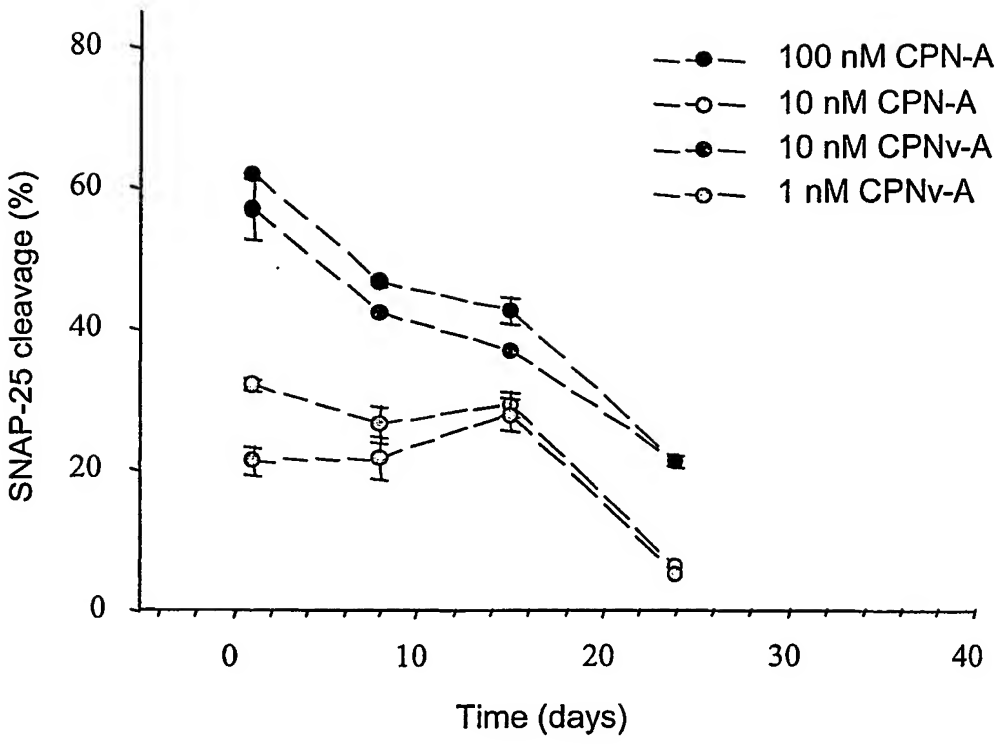

100 nM CPN-A
10 nM CPN-A
10 nM CPNv-A
1 nM CPNv-A
SNAP-25 cleavage (%)
0
20
40
60
80
0
10
20
30
40
Time (days)

Figure 14

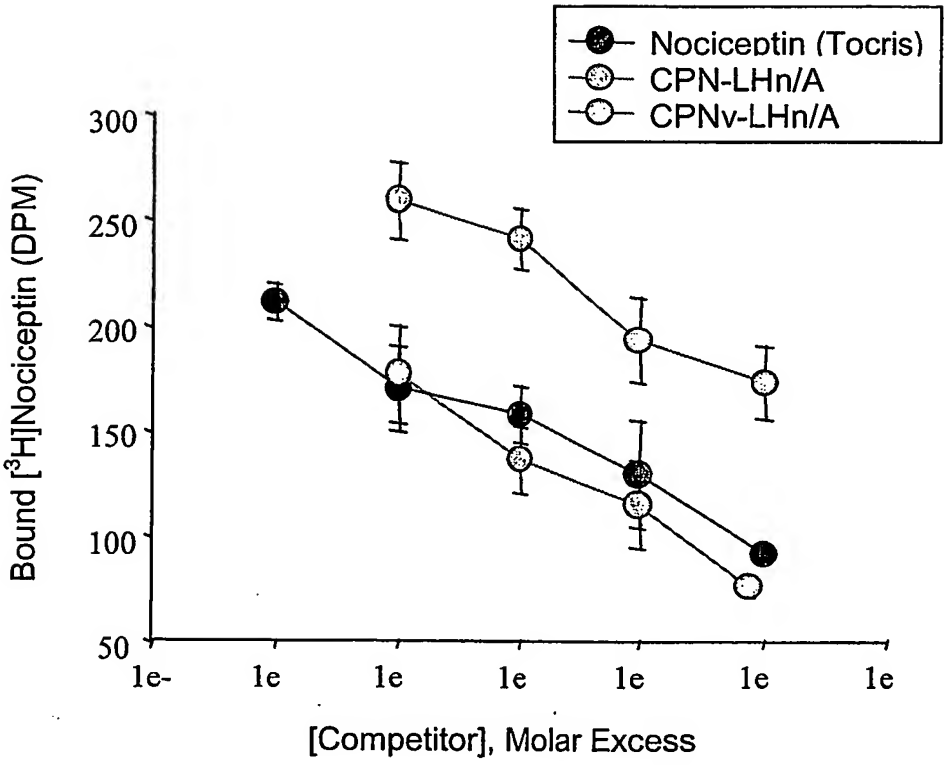

Nociceptin (Tocris)
CPN-LHn/A
CPNv-LHn/A
Bound [3H]Nociceptin (DPM)
300
250
200
150
100
50
1e-
1e
1e
1e
1e
1e
1e
[Competitor], Molar Excess

Figure 15

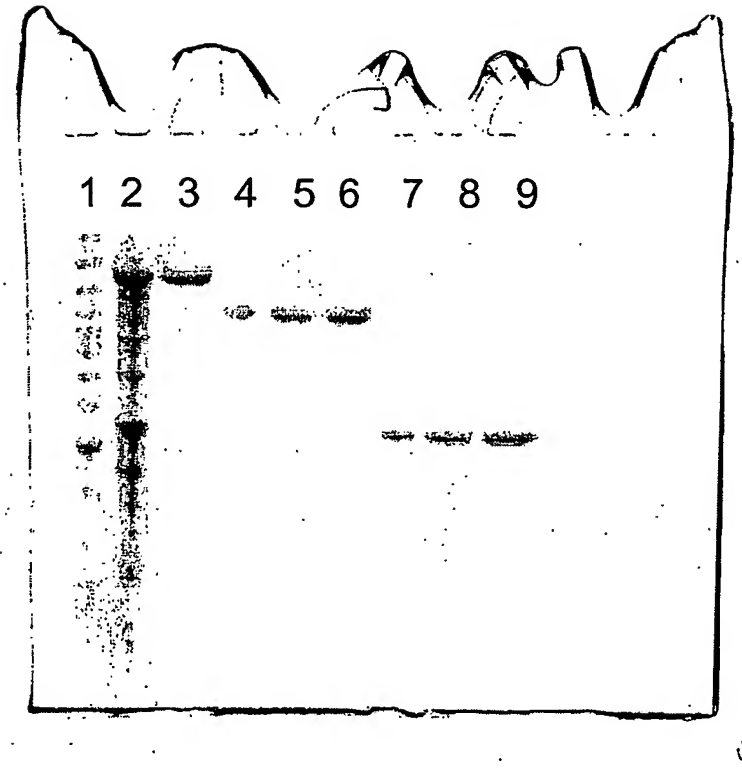


Figure 16

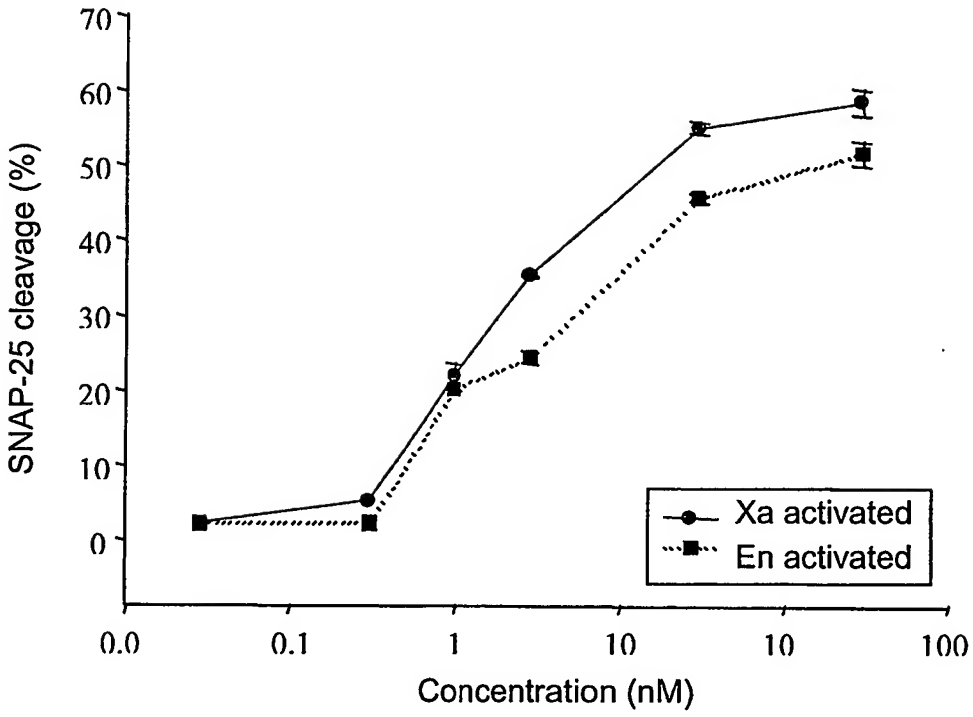

70
60
50
40
30
20
10
0
SNAP-25 cleavage (%)
0.0
0.1
1
10
10
100
Concentration (nM)
Xa activated
En activated

Figure 17

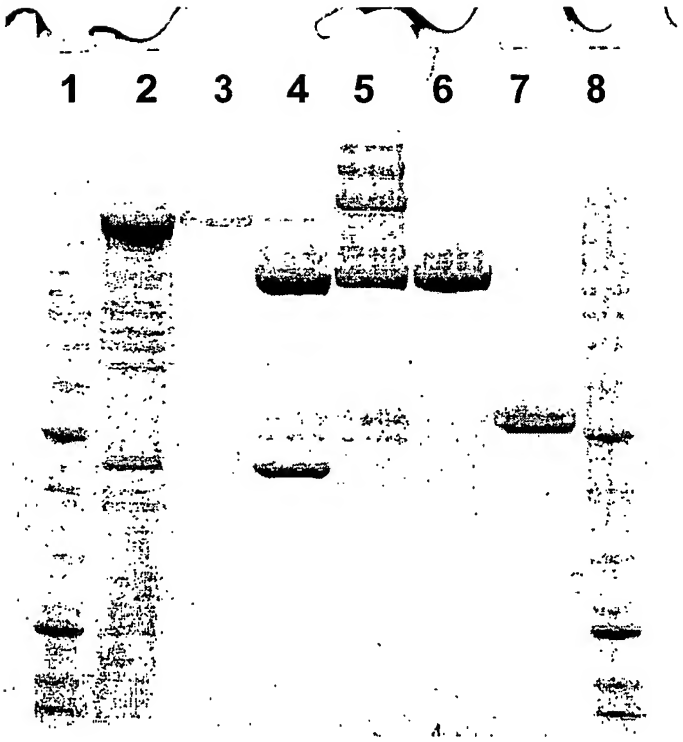


Figure 18

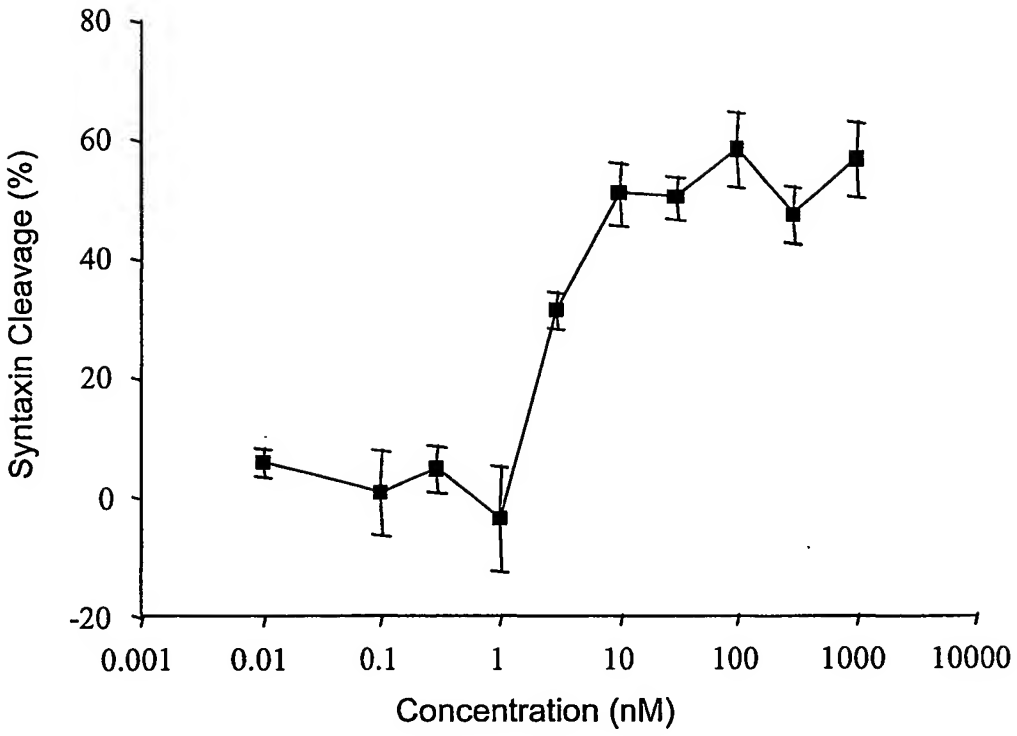

80
60
40
20
0
-20
Syntaxin Cleavage (%)
0.001
0.01
0.1
1
10
100
1000
10000
Concentration (nM)

Figure 19

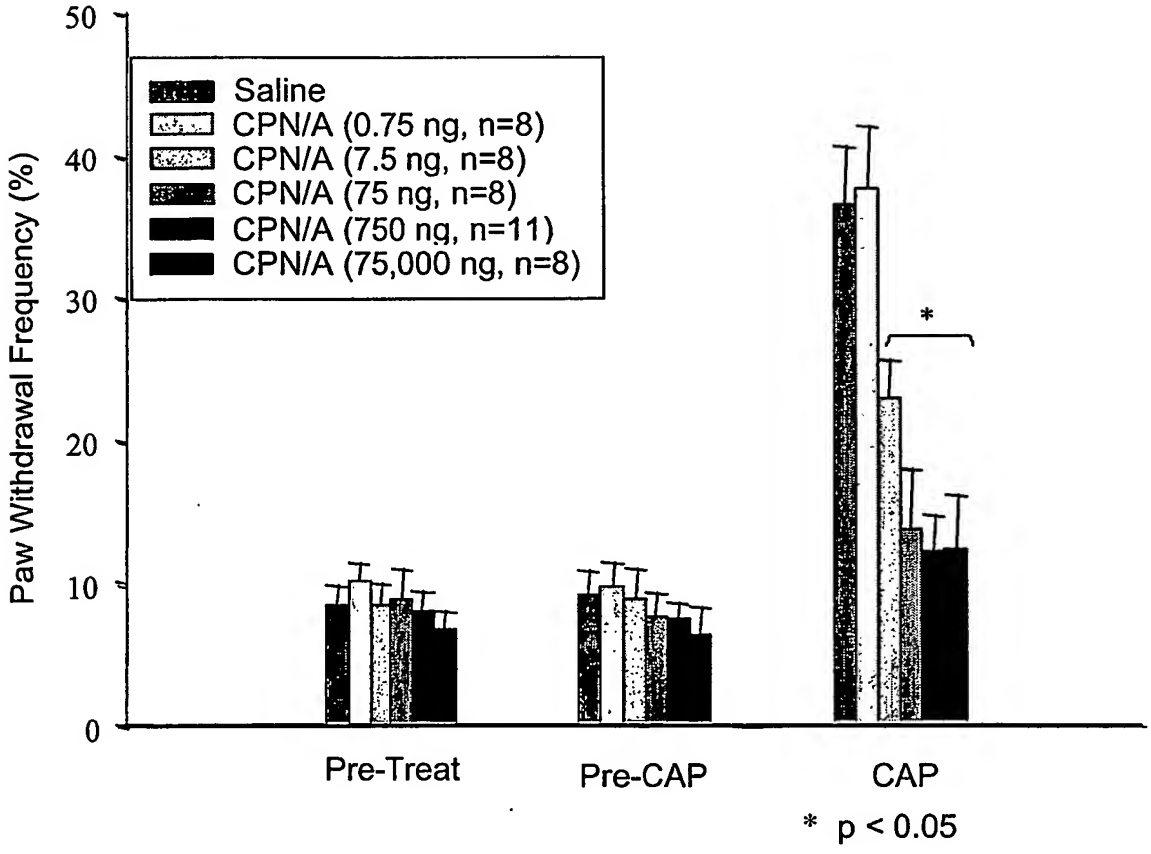

50
40
30
20
10
0
Paw Withdrawal Frequency (%)
Saline
CPN/A (0.75 ng, n=8)
CPN/A (7.5 ng, n=8)
CPN/A (75 ng, n=8)
CPN/A (750 ng, n=11)
CPN/A (75,000 ng, n=8)
*
Pre-Treat
Pre-CAP
CAP
* p < 0.05

Figure 20

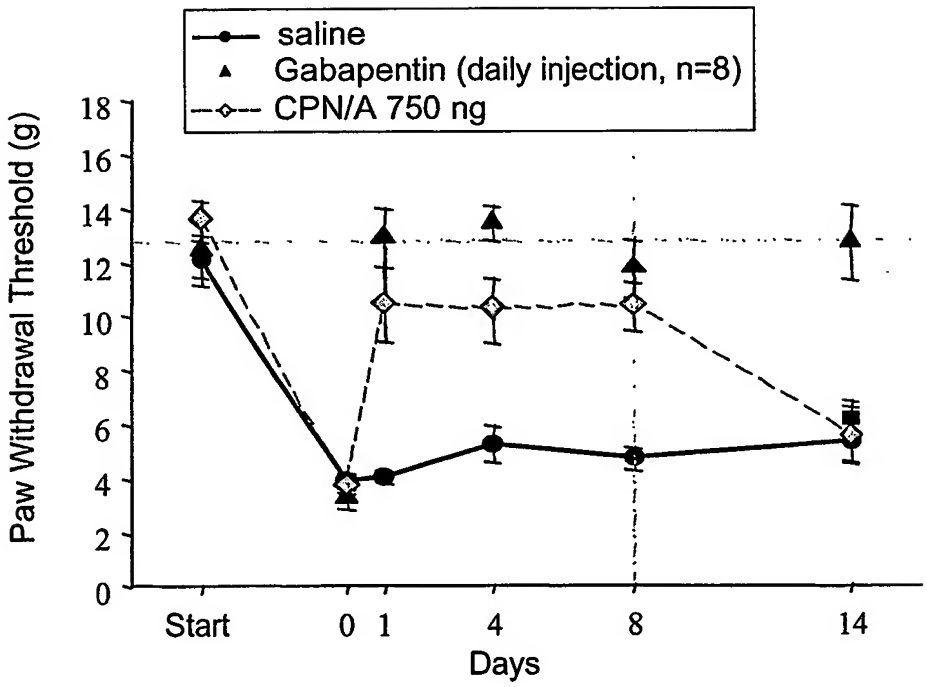

saline
Gabapentin (daily injection, n=8)
CPN/A 750 ng
Paw Withdrawal Threshold (g)
18
16
14
12
10
8
6
4
2
0
Start
0
1
4
8
14
Days

Figure 21

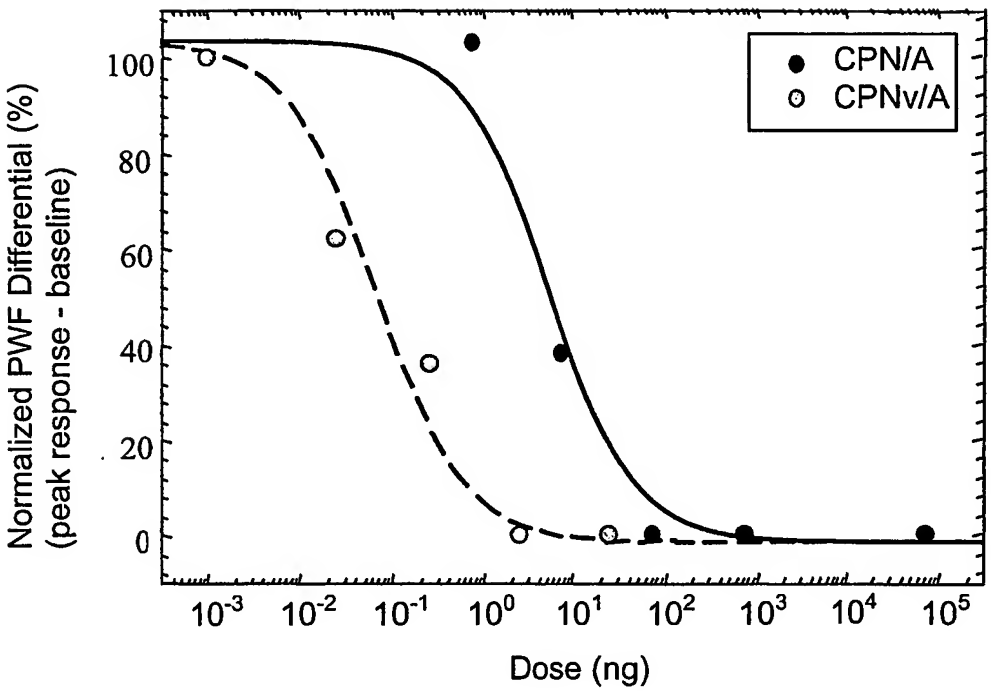

Normalized PWF Differential (%)
(peak response - baseline)
100
80
60
40
20
0
CPN/A
CPNv/A
10^{-3} 10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4} 10^{5}
Dose (ng)

Figure 22

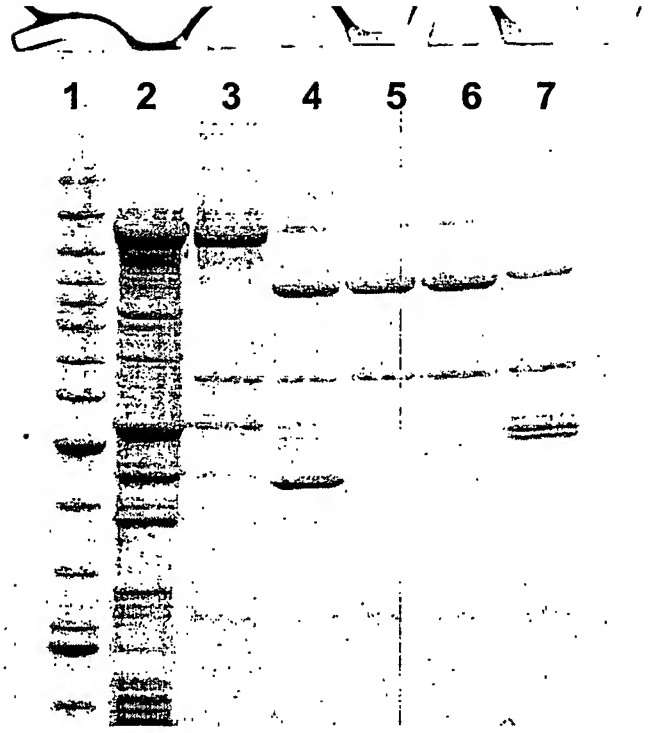


Figure 23

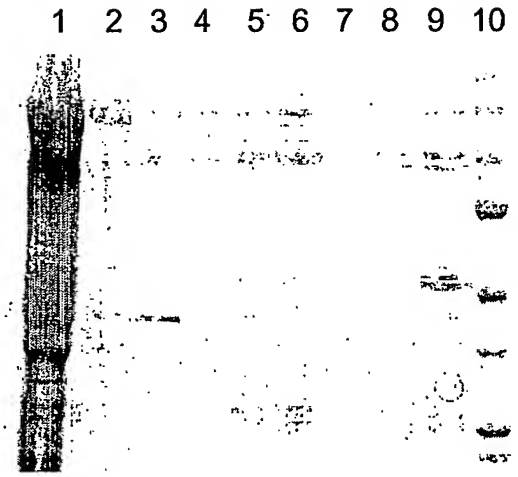


Figure 24

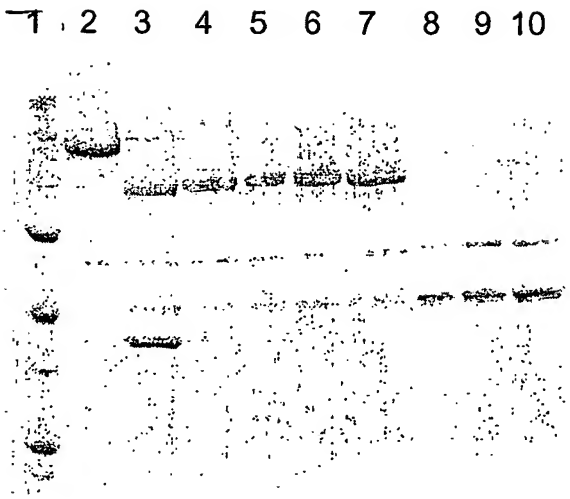


Figure 25

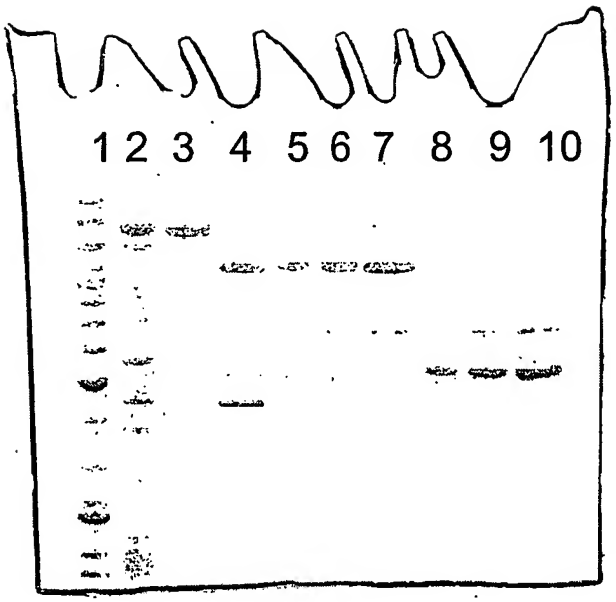


Figure 26

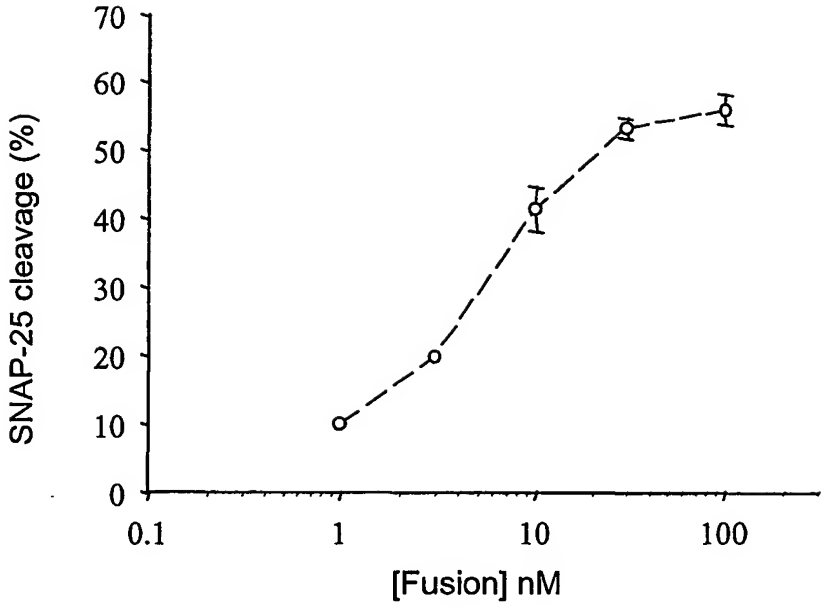


Figure 27

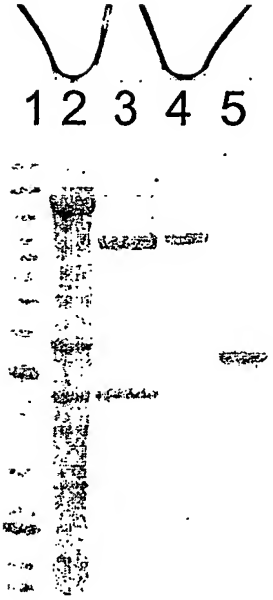
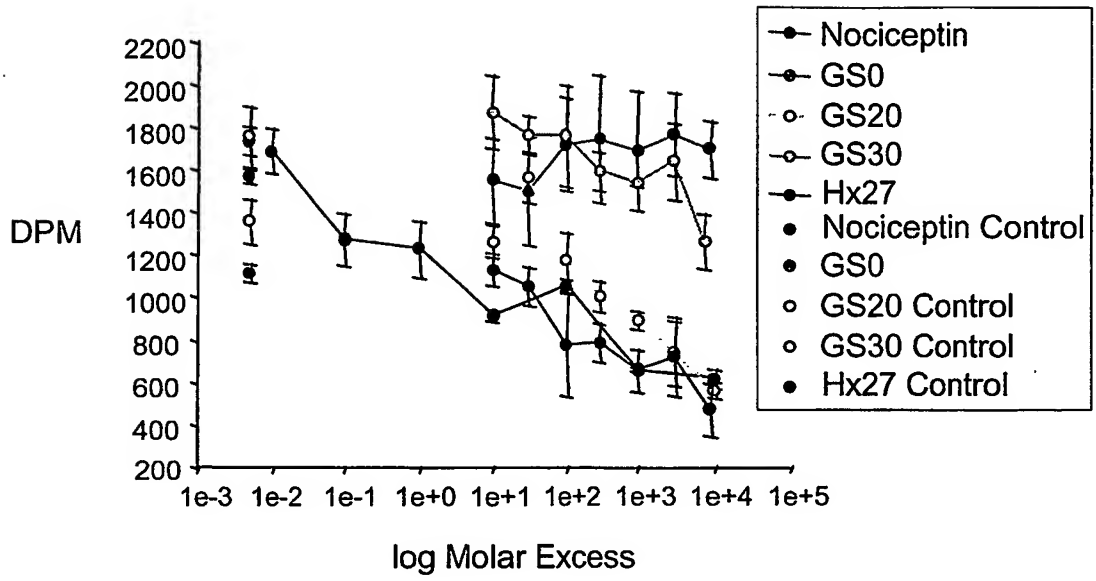


Figure 28


DPM
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
1e-3 1e-2 1e-1 1e+0 1e+1 1e+2 1e+3 1e+4 1e+5
log Molar Excess
Nociceptin
GS0
GS20
GS30
Hx27
Nociceptin Control
GS0
GS20 Control
GS30 Control
Hx27 Control

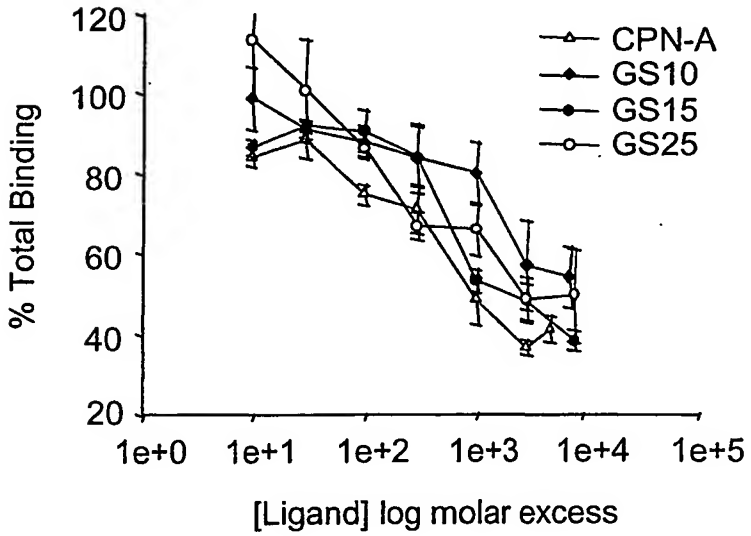
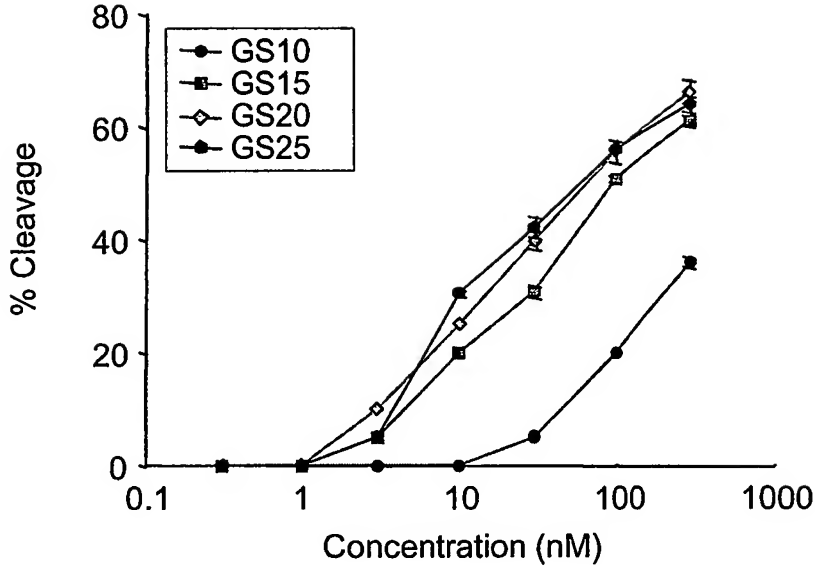

% Total Binding
120
100
80
60
40
20
1e+0 1e+1 1e+2 1e+3 1e+4 1e+5
[Ligand] log molar excess
CPN-A
GS10
GS15
GS25

Figure 29


80
60
40
20
0
% Cleavage
GS10
GS15
GS20
GS25
0.1
1
10
100
1000
Concentration (nM)

SEQUENCE LISTING

<110> Health Protection Agency
Allergan, Inc.
Chaddock, John
Foster, Keith
Marks, Philip
Stancombe, Patrick
Aoki, K Roger
Francis, Joseph
Steward, Lance

<120> Fusion Proteins

<130> P26885WO/MRM

<150> GB0426394.3
<151> 2004-12-01

<160> 88

<170> PatentIn version 3.3

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<213> Artificial Sequence

<220>
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attgcttaca tcaaaatccc gaacgctggc cagatgcagc cggtaaaggc attcaaaatc 120

cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

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gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

ttcactggtc tgttcgagtt ttacaagctg ctgtgcgtcg ac 1302

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gaaaacatct cgctggacct gatccagcag tactacctga cctttaattt cgacaacgag 180

ccggaaaaca tttctatcga aaacctgagc tctgatatca tcggccagct ggaactgatg 240

ccgaacatcg aacgtttccc aaacggtaaa aagtacgagc tggacaaata taccatgttc 300

cactacctgc gcgcgcagga atttgaacac ggcaaatccc gtatcgcact gactaactcc 360

gttaacgaag ctctgctcaa cccgtcccgt gtatacacct tcttctctag cgactacgtg 420

aaaaaggtca acaaagcgac tgaagctgca atgttcttgg gttgggttga acagcttgtt 480

tatgatttta ccgacgagac gtccgaagta tctactaccg acaaaattgc ggatatcact 540

atcatcatcc cgtacatcgg tccggctctg aacattggca acatgctgta caaagacgac 600

ttcgttggcg cactgatctt ctccggtgcg gtgatcctgc tggagttcat cccggaaatc 660

gccatcccgg tactgggcac ctttgctctg gtttcttaca ttgcaaacaa ggttctgact 720

gtacaaacca tcgacaacgc gctgagcaaa cgtaacgaaa aatgggatga agtttacaaa 780

tatatcgtga ccaactggct ggctaaggtt aatactcaga tcgacctcat ccgcaaaaaa 840

atgaaagaag cactggaaaa ccaggcggaa gctaccaagg caatcattaa ctaccagtac 900

aaccagtaca ccgaggaaga aaaaaacaac atcaacttca acatcgacga tctgtcctct 960

aaactgaacg aatccatcaa caaagctatg atcaacatca acaagttcct gaaccagtgc 1020

tctgtaagct atctgatgaa ctccatgatc ccgtacggtg ttaaacgtct ggaggacttc 1080

gatgcgtctc tgaaagacgc cctgctgaaa tacatttacg acaaccgtgg cactctgatc 1140

ggtcaggttg atcgtctgaa ggacaaagtg aacaatacct tatcgaccga catccctttt 1200

cagctcagta aatatgtcga taaccaacgc cttttgtcca ctctagacta gaagctt 1257

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<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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atcaccgacc gtatctggat catcccggaa cgttacacct tcggttacaa acctgaggac 180

ttcaacaaga gtagcgggat tttcaatcgt gacgtctgcg agtactatga tccagattat 240

ctgaatacca acgataagaa gaacatattc cttcagacta tgattaaact cttcaaccgt 300

atcaaaagca aaccgctcgg tgaaaaactc ctcgaaatga ttatcaacgg tatcccgtac 360

ctcggtgacc gtcgtgtccc gcttgaagag ttcaacacca acatcgcaag cgtcaccgtc 420

aacaaactca tcagcaaccc aggtgaagtc gaacgtaaaa aaggtatctt cgcaaacctc 480

atcatcttcg gtccgggtcc ggtcctcaac gaaaacgaaa ccatcgacat cggtatccag 540

aaccacttcg caagccgtga aggtttcggt ggtatcatgc agatgaaatt ctgcccggaa 600

tacgtcagtg tcttcaacaa cgtccaggaa aacaaaggtg caagcatctt caaccgtcgt 660

ggttacttca gcgacccggc actcatcctc atgcatgaac tcatccacgt cctccacggt 720

ctctacggta tcaaagttga cgacctcccg atcgtcccga acgagaagaa attcttcatg 780

cagagcaccg acgcaatcca ggctgaggaa ctctacacct tcggtggcca agacccaagt 840

atcataaccc cgtccaccga caaaagcatc tacgacaaag tcctccagaa cttcaggggt 900

atcgtggaca gactcaacaa agtcctcgtc tgcatcagcg acccgaacat caatatcaac 960

atatacaaga acaagttcaa agacaagtac aaattcgtcg aggacagcga aggcaaatac 1020

agcatcgacg tagaaagttt cgacaagctc tacaaaagcc tcatgttcgg tttcaccgaa 1080

accaacatcg ccgagaacta caagatcaag acaagggcaa gttacttcag cgacagcctc 1140

ccgcctgtca aaatcaagaa cctcttagac aacgagattt acacaattga agagggcttc 1200

aacatcagtg acaaagacat ggagaaggaa tacagaggtc agaacaaggc tatcaacaaa 1260

caggcatacg aggagatcag caaagaacac ctcgcagtct acaagatcca gatgtgcgtc 1320

gac 1323

<210> 4
<211> 1260
<212> DNA
<213> Artificial Sequence

<220>
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agtgacgacc tgagcaaaaa cgaacgtatc gaatacaaca cccagagcaa ctacatcgaa 120

aacgacttcc cgatcaacga actgatcctg gacaccgacc tgataagtaa aatcgaactg 180

ccgagcgaaa acaccgaaag tctgaccgac ttcaacgttg acgttccggt ttacgaaaaa 240

cagccggcta tcaagaaaat cttcaccgac gaaaacacca tcttccagta cctgtacagc 300

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aagaacctgc tgaactacat cgacgaaaac aagctgtacc tgatcggtag tgctgaatac 1140

gaaaaaagta aagtgaacaa atacctgaag accatcatgc cgttcgacct gagtatctac 1200

accaacgaca ccatcctgat cgaaatgttc aacaaataca actctctaga ctagaagctt 1260

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tttcgtatca ccggcaacat ttgggttatt ccggatcgtt ttagccgtaa cagcaacccg 180

aatctgaata aaccgccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat 240

ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc 300

atcaacagcc gtgaaattgg cgaagaactg atctatcgcc tgagcaccga tattccgttt 360

ccgggcaaca acaacacccc gatcaacacc tttgatttcg atgtggattt caacagcgtt 420

gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcgtg 480

attattaccg gtccgcgcga aaacattatt gatccggaaa ccagcacctt taaactgacc 540

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atcttcaccg aatttaacta tgcgaaaatc tataacgtgc agaaccgtaa aatctacctg 1140

agcaacgtgt ataccccggt gaccgcgaat attctggatg ataacgtgta cgatatccag 1200

aacggcttta acatcccgaa aagcaacctg aacgttctgt ttatgggcca gaacctgagc 1260

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tgcgtcgac 1329

<210> 6
<211> 1263
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tacccggata acgtgagcgt tgatcaggtg atcctgagca aaaacaccag cgaacatggt 180

cagctggatc tgctgtatcc gagcattgat agcgaaagcg aaattctgcc gggcgaaaac 240

caggtgtttt acgataaccg tacccagaac gtggattacc tgaacagcta ttactacctg 300

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gcgctggata acagcgcgaa agtttacacc tattttccga ccctggcgaa caaagttaat 420

gcgggtgttc agggcggtct gtttctgatg tgggcgaacg atgtggtgga agatttcacc 480

accaacatcc tgcgtaaaga taccctggat aaaatcagcg atgttagcgc gattattccg 540

tatattggtc cggcgctgaa cattagcaat agcgtgcgtc gtggcaattt taccgaagcg 600

tttgcggtta ccggtgtgac cattctgctg gaagcgtttc cggaatttac cattccggcg 660

ctgggtgcgt ttgtgatcta tagcaaagtg caggaacgca acgaaatcat caaaaccatc 720

gataactgcc tggaacagcg tattaaacgc tggaaagata gctatgaatg gatgatgggc 780

acctggctga gccgtattat cacccagttc aacaacatca gctaccagat gtacgatagc 840

ctgaactatc aggcgggtgc gattaaagcg aaaatcgatc tggaatacaa aaaatacagc 900

ggcagcgata aagaaaacat caaaagccag gttgaaaacc tgaaaaacag cctggatgtg 960

aaaattagcg aagcgatgaa taacatcaac aaattcatcc gcgaatgcag cgtgacctac 1020

ctgttcaaaa acatgctgcc gaaagtgatc gatgaactga acgaatttga tcgcaacacc 1080

aaagcgaaac tgatcaacct gatcgatagc cacaacatta ttctggtggg cgaagtggat 1140

aaactgaaag cgaaagttaa caacagcttc cagaacacca tcccgtttaa catcttcagc 1200

tataccaaca acagcctgct gaaagatatc atcaacgaat acttcaatct agactagaag 1260

ctt 1263

<210> 7
<211> 207
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 7
ggatccacgc acgtcgacgg catcattacc tccaaaacta aatctctgat cgaaggtcgt 60

tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaat tagctaacca ggcgctagcg 120

ggcggtggcg gtagcggcgg tggcggtagc ggcggtggcg gtagcgcact agtgctgcag 180

acgcacggtc tagaatgata aaagctt 207

<210> 8

<211> 108
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 8
ggatccacgc acgtcgacgg catcattacc tccaaaacta aatctctgat agaaggtaga 60

aacaaagcgc tgaacctgca gacgcacggt ctagaatgat aaaagctt 108

<210> 9
<211> 186
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 9
catatgaata acctcgggat tgagggtcgt tttggcggtt tcacgggcgc acgcaaatca 60

gcgcgtaaat tagctaacca gactagtggc ggtgggggta gtggcggtgg cggttcgggc 120

gggggtggga gccctagggg atccgtcgac ctgcagggtc tagaagcgct agcgtgataa 180

aagctt 186

<210> 10
<211> 180
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 10
ggatccacgc acgtcgacgc gattgatggt cgttttggcg gtttcacggg cgcacgcaaa 60

tcagcgcgta aattagctaa ccaggcgcta gcgggcggtg gcggtagcgg cggtggcggt 120

agcggcggtg gcggtagcgc actagtgctg cagacgcacg gtctagaatg ataaaagctt 180

<210> 11
<211> 249
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 11
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tacggtggtt tcatgacctc tgaaaaatct cagaccccgc tggttaccct gttcaaaaac 120

gctatcatca aaaacgctta caaaaaaggt gaagcgctag cgggtggtgg tggttctggt 180

ggtggtggtt ctggtggtgg tggttctgca ctagtgctgc agacgcacgg tctagaatga 240

taaaagctt 249

<210> 12
<211> 207
<212> DNA
<213> Artificial Sequence .

<220>
<223> Synthetic

<400> 12
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tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaac gtaagaacca ggcgctagcg 120

ggcggtggcg gtagcggcgg tggcggtagc ggcggtggcg gtagcgcact agtgctgcag 180

acgcacggtc tagaatgata aaagctt 207

<210> 13
<211> 2709
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 13
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attgcttaca tcaaaatccc gaacgctggc cagatgcagc cggtaaaggc attcaaaatc 120

cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

ttcactggtc tgttcgagtt ttacaagctg ctgtgcgtcg acggcatcat tacctccaaa 1320

actaaatctc tgatagaagg tagatttggc ggtttcacgg gcgcacgcaa atcagcgcgt 1380

aaattagcta accaggcgct agcgggcggt ggcggtagcg gcggtggcgg tagcggcggt 1440

ggcggtagcg cactagtgct gcagtgtatc aaggttaaca actgggattt attcttcagc 1500

ccgagtgaag acaacttcac caacgacctg aacaaaggtg aagaaatcac ctcagatact 1560

aacatcgaag cagccgaaga aaacatctcg ctggacctga tccagcagta ctacctgacc 1620

tttaatttcg acaacgagcc ggaaaacatt tctatcgaaa acctgagctc tgatatcatc 1680

ggccagctgg aactgatgcc gaacatcgaa cgtttcccaa acggtaaaaa gtacgagctg 1740

gacaaatata ccatgttcca ctacctgcgc gcgcaggaat ttgaacacgg caaatcccgt 1800

atcgcactga ctaactccgt taacgaagct ctgctcaacc cgtcccgtgt atacaccttc 1860

ttctctagcg actacgtgaa aaaggtcaac aaagcgactg aagctgcaat gttcttgggt 1920

tgggttgaac agcttgttta tgattttacc gacgagacgt ccgaagtatc tactaccgac 1980

aaaattgcgg atatcactat catcatcccg tacatcggtc cggctctgaa cattggcaac 2040

atgctgtaca aagacgactt cgttggcgca ctgatcttct ccggtgcggt gatcctgctg 2100

gagttcatcc cggaaatcgc catcccggta ctgggcacct ttgctctggt ttcttacatt 2160

gcaaacaagg ttctgactgt acaaaccatc gacaacgcgc tgagcaaacg taacgaaaaa 2220

tgggatgaag tttacaaata tatcgtgacc aactggctgg ctaaggttaa tactcagatc 2280

gacctcatcc gcaaaaaaat gaaagaagca ctggaaaacc aggcggaagc taccaaggca 2340

atcattaact accagtacaa ccagtacacc gaggaagaaa aaaacaacat caacttcaac 2400

atcgacgatc tgtcctctaa actgaacgaa tccatcaaca aagctatgat caacatcaac 2460

aagttcctga accagtgctc tgtaagctat ctgatgaact ccatgatccc gtacggtgtt 2520

aaacgtctgg aggacttcga tgcgtctctg aaagacgccc tgctgaaata catttacgac 2580

aaccgtggca ctctgatcgg tcaggttgat cgtctgaagg acaaagtgaa caatacctta 2640

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ctagactag 2709

<210> 14
<211> 902
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 14

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

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Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430
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Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
450 455 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465 470 475 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
485 490 495

Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
500 505 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
515 520 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
530 535 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
545 550 555 560

Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
565 570 575

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
580 585 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
595 600 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
610 615 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
625 630 635 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
645 650 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
660 665 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val

675 680 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
690 695 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705 710 715 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
725 730 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
740 745 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
755 760 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
770 775 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785 790 795 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Asp
900

<210> 15
<211> 2736

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 15
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gctaaccaga ctagtggcgg tgggggtagt ggcggtggcg gttcgggcgg gggtgggagc 120

cctaggggat ccatggagtt cgttaacaaa cagttcaact ataaagaccc agttaacggt 180

gttgacattg cttacatcaa aatcccgaac gctggccaga tgcagccggt aaaggcattc 240

aaaatccaca acaaaatctg ggttatcccg gaacgtgata cctttactaa cccggaagaa 300

ggtgacctga acccgccacc ggaagcgaaa caggtgccgg tatcttacta tgactccacc 360

tacctgtcta ccgataacga aaaggacaac tacctgaaag gtgttactaa actgttcgag 420

cgtatttact ccaccgacct gggccgtatg ctgctgacta gcatcgttcg cggtatcccg 480

ttctggggcg gttctaccat cgataccgaa ctgaaagtaa tcgacactaa ctgcatcaac 540

gttattcagc cggacggttc ctatcgttcc gaagaactga acctggtgat catcggcccg 600

tctgctgata tcatccagtt cgagtgtaag agctttggtc acgaagttct gaacctcacc 660

cgtaacggct acggttccac tcagtacatc cgtttctctc cggacttcac cttcggtttt 720

gaagaatccc tggaagtaga cacgaaccca ctgctgggcg ctggtaaatt cgcaactgat 780

cctgcggtta ccctggctca cgaactgatt catgcaggcc accgcctgta cggtatcgcc 840

atcaatccga accgtgtctt caaagttaac accaacgcgt attacgagat gtccggtctg 900

gaagttagct tcgaagaact gcgtactttt ggcggtcacg acgctaaatt catcgactct 960

ctgcaagaaa acgagttccg tctgtactac tataacaagt tcaaagatat cgcatccacc 1020

ctgaacaaag cgaaatccat cgtgggtacc actgcttctc tccagtacat gaagaacgtt 1080

tttaaagaaa aatacctgct cagcgaagac acctccggca aattctctgt agacaagttg 1140

aaattcgata aactttacaa aatgctgact gaaatttaca ccgaagacaa cttcgttaag 1200

ttctttaaag ttctgaaccg caaaacctat ctgaacttcg acaaggcagt attcaaaatc 1260

aacatcgtgc cgaaagttaa ctacactatc tacgatggtt tcaacctgcg taacaccaac 1320

ctggctgcta attttaacgg ccagaacacg gaaatcaaca acatgaactt cacaaaactg 1380

aaaaacttca ctggtctgtt cgagttttac aagctgctgt gcgtcgacgg catcattacc 1440

tccaaaacta aatctctgat agaaggtaga aacaaagcgc tgaacgacct ctgtatcaag 1500

gttaacaact gggatttatt cttcagcccg agtgaagaca acttcaccaa cgacctgaac 1560

aaaggtgaag aaatcacctc agatactaac atcgaagcag ccgaagaaaa catctcgctg 1620

gacctgatcc agcagtacta cctgaccttt aatttcgaca acgagccgga aaacatttct 1680

atcgaaaacc tgagctctga tatcatcggc cagctggaac tgatgccgaa catcgaacgt 1740

ttcccaaacg gtaaaaagta cgagctggac aaatatacca tgttccacta cctgcgcgcg 1800

caggaatttg aacacggcaa atcccgtatc gcactgacta actccgttaa cgaagctctg 1860

ctcaacccgt cccgtgtata caccttcttc tctagcgact acgtgaaaaa ggtcaacaaa 1920

gcgactgaag ctgcaatgtt cttgggttgg gttgaacagc ttgtttatga ttttaccgac 1980

gagacgtccg aagtatctac taccgacaaa attgcggata tcactatcat catcccgtac 2040

atcggtccgg ctctgaacat tggcaacatg ctgtacaaag acgacttcgt tggcgcactg 2100

atcttctccg gtgcggtgat cctgctggag ttcatcccgg aaatcgccat cccggtactg 2160

ggcacctttg ctctggtttc ttacattgca aacaaggttc tgactgtaca aaccatcgac 2220

aacgcgctga gcaaacgtaa cgaaaaatgg gatgaagttt acaaatatat cgtgaccaac 2280

tggctggcta aggttaatac tcagatcgac ctcatccgca aaaaaatgaa agaagcactg 2340

gaaaaccagg cggaagctac caaggcaatc attaactacc agtacaacca gtacaccgag 2400

gaagaaaaaa acaacatcaa cttcaacatc gacgatctgt cctctaaact gaacgaatcc 2460

atcaacaaag ctatgatcaa catcaacaag ttcctgaacc agtgctctgt aagctatctg 2520

atgaactcca tgatcccgta cggtgttaaa cgtctggagg acttcgatgc gtctctgaaa 2580

gacgccctgc tgaaatacat ttacgacaac cgtggcactc tgatcggtca ggttgatcgt 2640

ctgaaggaca aagtgaacaa taccttatcg accgacatcc cttttcagct cagtaaatat 2700

gtcgataacc aacgcctttt gtccactcta gactag 2736

<210> 16
<211> 911
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 16

Leu Gly Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser
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Ala Arg Lys Leu Ala Asn Gln Thr Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Pro Arg Gly Ser Met Glu Phe Val
35 40 45

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Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly Val Asp Ile Ala
    50                  55                  60

Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro Val Lys Ala Phe
65                  70                  75                  80

Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg Asp Thr Phe Thr
            85                  90                  95

Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu Ala Lys Gln Val
        100                 105                 110

Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr Asp Asn Glu Lys
    115                 120                 125

Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu Arg Ile Tyr Ser
    130                 135                 140

Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val Arg Gly Ile Pro
145                 150                 155                 160

Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys Val Ile Asp Thr
                165                 170                 175

Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr Arg Ser Glu Glu
        180                 185                 190

Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile Ile Gln Phe Glu
    195                 200                 205

Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr Arg Asn Gly Tyr
    210                 215                 220

Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe Thr Phe Gly Phe
225                 230                 235                 240

Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu Gly Ala Gly Lys
                245                 250                 255

Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu Leu Ile His Ala
        260                 265                 270

Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn Arg Val Phe Lys
    275                 280                 285

Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu Glu Val Ser Phe
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290 295 300

Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys Phe Ile Asp Ser
305 310 315 320

Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn Lys Phe Lys Asp
325 330 335

Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val Gly Thr Thr Ala
340 345 350

Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys Tyr Leu Leu Ser
355 360 365

Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu Lys Phe Asp Lys
370 375 380

Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp Asn Phe Val Lys
385 390 395 400

Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn Phe Asp Lys Ala
405 410 415

Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr Thr Ile Tyr Asp
420 425 430

Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn Phe Asn Gly Gln
435 440 445

Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu Lys Asn Phe Thr
450 455 460

Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Asp Gly Ile Ile Thr
465 470 475 480

Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg Asn Lys Ala Leu Asn Asp
485 490 495

Leu Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu
500 505 510

Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp
515 520 525

Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln
530 535 540

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Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser
545                 550                 555                 560

Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro
                565                 570                 575

Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr
            580                 585                 590

Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser
        595                 600                 605

Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser
    610                 615                 620

Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys
625                 630                 635                 640

Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr
                645                 650                 655

Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala
            660                 665                 670

Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly
        675                 680                 685

Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly
    690                 695                 700

Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu
705                 710                 715                 720

Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val
                725                 730                 735

Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu
            740                 745                 750

Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln
        755                 760                 765

Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala
    770                 775                 780
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Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu
785 790 795 800

Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys
805 810 815

Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu
820 825 830

Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly
835 840 845

Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu
850 855 860

Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg
865 870 875 880

Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln
885 890 895

Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
900 905 910

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<211> 2715
<212> DNA
<213> Artificial Sequence

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<223> Synthetic

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tttcgtatca ccggcaacat ttgggttatt ccggatcgtt ttagccgtaa cagcaacccg 180

aatctgaata aaccgccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat 240

ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc 300

atcaacagcc gtgaaattgg cgaagaactg atctatcgcc tgagcaccga tattccgttt 360

ccgggcaaca acaacacccc gatcaacacc tttgatttcg atgtggattt caacagcgtt 420

gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcgtg 480

attattaccg gtccgcgcga aaacattatt gatccggaaa ccagcacctt taaactgacc 540

aacaacacct ttgcggcgca ggaaggtttt ggcgcgctga gcattattag cattagcccg 600

cgctttatgc tgacctatag caacgcgacc aacgatgttg gtgaaggccg tttcagcaaa 660

agcgaatttt gcatggaccc gatcctgatc ctgatgcatg aactgaacca tgcgatgcat 720

aacctgtatg gcatcgcgat tccgaacgat cagaccatta gcagcgtgac cagcaacatc 780

ttttacagcc agtacaacgt gaaactggaa tatgcggaaa tctatgcgtt tggcggtccg 840

accattgatc tgattccgaa aagcgcgcgc aaatacttcg aagaaaaagc gctggattac 900

tatcgcagca ttgcgaaacg tctgaacagc attaccaccg cgaatccgag cagcttcaac 960

aaatatatcg gcgaatataa acagaaactg atccgcaaat atcgctttgt ggtggaaagc 1020

agcggcgaag ttaccgttaa ccgcaataaa ttcgtggaac tgtacaacga actgacccag 1080

atcttcaccg aatttaacta tgcgaaaatc tataacgtgc agaaccgtaa aatctacctg 1140

agcaacgtgt ataccccggt gaccgcgaat attctggatg ataacgtgta cgatatccag 1200

aacggcttta acatcccgaa aagcaacctg aacgttctgt ttatgggcca gaacctgagc 1260

cgtaatccgg cgctgcgtaa agtgaacccg gaaaacatgc tgtacctgtt caccaaattt 1320

tgcgtcgacg cgatagatgg tagatttggc ggtttcacgg gcgcacgcaa atcagcgcgt 1380

aaattagcta accaggcgct agcgggcggt ggcggtagcg gcggtggcgg tagcggcggt 1440

ggcggtagcg cactagtgct gcagtgtcgt gaactgctgg tgaaaaacac cgatctgccg 1500

tttattggcg atatcagcga tgtgaaaacc gatatcttcc tgcgcaaaga tatcaacgaa 1560

gaaaccgaag tgatctacta cccggataac gtgagcgttg atcaggtgat cctgagcaaa 1620

aacaccagcg aacatggtca gctggatctg ctgtatccga gcattgatag cgaaagcgaa 1680

attctgccgg gcgaaaacca ggtgttttac gataaccgta cccagaacgt ggattacctg 1740

aacagctatt actacctgga aagccagaaa ctgagcgata acgtggaaga ttttaccttt 1800

acccgcagca ttgaagaagc gctggataac agcgcgaaag tttacaccta ttttccgacc 1860

ctggcgaaca aagttaatgc gggtgttcag ggcggtctgt ttctgatgtg ggcgaacgat 1920

gtggtggaag atttcaccac caacatcctg cgtaaagata ccctggataa aatcagcgat 1980

gttagcgcga ttattccgta tattggtccg gcgctgaaca ttagcaatag cgtgcgtcgt 2040

ggcaatttta ccgaagcgtt tgcggttacc ggtgtgacca ttctgctgga agcgtttccg 2100

gaatttacca ttccggcgct gggtgcgttt gtgatctata gcaaagtgca ggaacgcaac 2160

gaaatcatca aaaccatcga taactgcctg gaacagcgta ttaaacgctg gaaagatagc 2220

tatgaatgga tgatgggcac ctggctgagc cgtattatca cccagttcaa caacatcagc 2280

taccagatgt acgatagcct gaactatcag gcgggtgcga ttaaagcgaa aatcgatctg 2340

gaatacaaaa aatacagcgg cagcgataaa gaaaacatca aaagccaggt tgaaaacctg 2400

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gaatgcagcg tgacctacct gttcaaaaac atgctgccga aagtgatcga tgaactgaac 2520

gaatttgatc gcaacaccaa agcgaaactg atcaacctga tcgatagcca caacattatt 2580

ctggtgggcg aagtggataa actgaaagcg aaagttaaca acagcttcca gaacaccatc 2640

ccgtttaaca tcttcagcta taccaacaac agcctgctga aagatatcat caacgaatac 2700

ttcaatctag actag 2715

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<211> 904
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 18

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Pro Val Asp Asn Lys Asn Ile Leu Tyr Leu Asp Thr His Leu Asn Thr
20 25 30

Leu Ala Asn Glu Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn Ile Trp
35 40 45

Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys
50 55 60

Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr
65 70 75 80

Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys
85 90 95

Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr
100 105 110

Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile
115 120 125

Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr
130 135 140

Arg Gln Gly Asn Asn Trp Val Lys Thr Gly Ser Ile Asn Pro Ser Val
145 150 155 160

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Ile Ile Thr Gly Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr Ser Thr
                165                 170                 175

Phe Lys Leu Thr Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe Gly Ala
            180                 185                 190

Leu Ser Ile Ile Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr Ser Asn
        195                 200                 205

Ala Thr Asn Asp Val Gly Glu Gly Arg Phe Ser Lys Ser Glu Phe Cys
    210                 215                 220

Met Asp Pro Ile Leu Ile Leu Met His Glu Leu Asn His Ala Met His
225                 230                 235                 240

Asn Leu Tyr Gly Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser Ser Val
                245                 250                 255

Thr Ser Asn Ile Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu Tyr Ala
            260                 265                 270

Glu Ile Tyr Ala Phe Gly Gly Pro Thr Ile Asp Leu Ile Pro Lys Ser
        275                 280                 285

Ala Arg Lys Tyr Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg Ser Ile
    290                 295                 300

Ala Lys Arg Leu Asn Ser Ile Thr Thr Ala Asn Pro Ser Ser Phe Asn
305                 310                 315                 320

Lys Tyr Ile Gly Glu Tyr Lys Gln Lys Leu Ile Arg Lys Tyr Arg Phe
                325                 330                 335

Val Val Glu Ser Ser Gly Glu Val Thr Val Asn Arg Asn Lys Phe Val
            340                 345                 350

Glu Leu Tyr Asn Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn Tyr Ala
        355                 360                 365

Lys Ile Tyr Asn Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn Val Tyr
    370                 375                 380

Thr Pro Val Thr Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp Ile Gln
385                 390                 395                 400
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Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly
                405                 410                 415

Gln Asn Leu Ser Arg Asn Pro Ala Leu Arg Lys Val Asn Pro Glu Asn
            420                 425                 430

Met Leu Tyr Leu Phe Thr Lys Phe Cys Val Asp Ala Ile Asp Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Arg Glu Leu Leu Val Lys Asn
                485                 490                 495

Thr Asp Leu Pro Phe Ile Gly Asp Ile Ser Asp Val Lys Thr Asp Ile
            500                 505                 510

Phe Leu Arg Lys Asp Ile Asn Glu Glu Thr Glu Val Ile Tyr Tyr Pro
        515                 520                 525

Asp Asn Val Ser Val Asp Gln Val Ile Leu Ser Lys Asn Thr Ser Glu
    530                 535                 540

His Gly Gln Leu Asp Leu Leu Tyr Pro Ser Ile Asp Ser Glu Ser Glu
545                 550                 555                 560

Ile Leu Pro Gly Glu Asn Gln Val Phe Tyr Asp Asn Arg Thr Gln Asn
                565                 570                 575

Val Asp Tyr Leu Asn Ser Tyr Tyr Tyr Leu Glu Ser Gln Lys Leu Ser
            580                 585                 590

Asp Asn Val Glu Asp Phe Thr Phe Thr Arg Ser Ile Glu Glu Ala Leu
        595                 600                 605

Asp Asn Ser Ala Lys Val Tyr Thr Tyr Phe Pro Thr Leu Ala Asn Lys
    610                 615                 620

Val Asn Ala Gly Val Gln Gly Gly Leu Phe Leu Met Trp Ala Asn Asp
625                 630                 635                 640
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Val Val Glu Asp Phe Thr Thr Asn Ile Leu Arg Lys Asp Thr Leu Asp
                645                 650                 655

Lys Ile Ser Asp Val Ser Ala Ile Ile Pro Tyr Ile Gly Pro Ala Leu
            660                 665                 670

Asn Ile Ser Asn Ser Val Arg Arg Gly Asn Phe Thr Glu Ala Phe Ala
        675                 680                 685

Val Thr Gly Val Thr Ile Leu Leu Glu Ala Phe Pro Glu Phe Thr Ile
    690                 695                 700

Pro Ala Leu Gly Ala Phe Val Ile Tyr Ser Lys Val Gln Glu Arg Asn
705                 710                 715                 720

Glu Ile Ile Lys Thr Ile Asp Asn Cys Leu Glu Gln Arg Ile Lys Arg
                725                 730                 735

Trp Lys Asp Ser Tyr Glu Trp Met Met Gly Thr Trp Leu Ser Arg Ile
            740                 745                 750

Ile Thr Gln Phe Asn Asn Ile Ser Tyr Gln Met Tyr Asp Ser Leu Asn
        755                 760                 765

Tyr Gln Ala Gly Ala Ile Lys Ala Lys Ile Asp Leu Glu Tyr Lys Lys
    770                 775                 780

Tyr Ser Gly Ser Asp Lys Glu Asn Ile Lys Ser Gln Val Glu Asn Leu
785                 790                 795                 800

Lys Asn Ser Leu Asp Val Lys Ile Ser Glu Ala Met Asn Asn Ile Asn
                805                 810                 815

Lys Phe Ile Arg Glu Cys Ser Val Thr Tyr Leu Phe Lys Asn Met Leu
            820                 825                 830

Pro Lys Val Ile Asp Glu Leu Asn Glu Phe Asp Arg Asn Thr Lys Ala
        835                 840                 845

Lys Leu Ile Asn Leu Ile Asp Ser His Asn Ile Ile Leu Val Gly Glu
    850                 855                 860

Val Asp Lys Leu Lys Ala Lys Val Asn Asn Ser Phe Gln Asn Thr Ile
865                 870                 875                 880

Pro Phe Asn Ile Phe Ser Tyr Thr Asn Asn Ser Leu Leu Lys Asp Ile
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885 890 895

Ile Asn Glu Tyr Phe Asn Leu Asp
900

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<211> 2742
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 19
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tttcgtatca ccggcaacat ttgggttatt ccggatcgtt ttagccgtaa cagcaacccg 180

aatctgaata aaccgccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat 240

ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc 300

atcaacagcc gtgaaattgg cgaagaactg atctatcgcc tgagcaccga tattccgttt 360

ccgggcaaca acaacacccc gatcaacacc tttgatttcg atgtggattt caacagcgtt 420

gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcgtg 480

attattaccg gtccgcgcga aaacattatt gatccggaaa ccagcacctt taaactgacc 540

aacaacacct ttgcggcgca ggaaggtttt ggcgcgctga gcattattag cattagcccg 600

cgctttatgc tgacctatag caacgcgacc aacgatgttg gtgaaggccg tttcagcaaa 660

agcgaatttt gcatggaccc gatcctgatc ctgatgcatg aactgaacca tgcgatgcat 720

aacctgtatg gcatcgcgat tccgaacgat cagaccatta gcagcgtgac cagcaacatc 780

ttttacagcc agtacaacgt gaaactggaa tatgcggaaa tctatgcgtt tggcggtccg 840

accattgatc tgattccgaa aagcgcgcgc aaatacttcg aagaaaaagc gctggattac 900

tatcgcagca ttgcgaaacg tctgaacagc attaccaccg cgaatccgag cagcttcaac 960

aaatatatcg gcgaatataa acagaaactg atccgcaaat atcgctttgt ggtggaaagc 1020

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atcttcaccg aatttaacta tgcgaaaatc tataacgtgc agaaccgtaa aatctacctg 1140

agcaacgtgt ataccccggt gaccgcgaat attctggatg ataacgtgta cgatatccag 1200

aacggcttta acatcccgaa aagcaacctg aacgttctgt ttatgggcca gaacctgagc 1260

cgtaatccgg cgctgcgtaa agtgaacccg gaaaacatgc tgtacctgtt caccaaattt 1320

tgcgtcgacg gcatcattac caccaaaact aaatctctga ctagaaggtag atttggcggt 1380

ttcacgggcg cacgcaaatc agcgcgtaaa ttagctaacc aggcgctagc gggcggtggc 1440

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atcttcctgc gcaaagatat caacgaagaa accgaagtga tctactaccc ggataacgtg 1620

agcgttgatc aggtgatcct gagcaaaaac accagcgaac atggtcagct ggatctgctg 1680

tatccgagca ttgatagcga aagcgaaatt ctgccgggcg aaaaccaggt gttttacgat 1740

aaccgtaccc agaacgtgga ttacctgaac agctattact acctggaaag ccagaaactg 1800

agcgataacg tggaagattt tacctttacc cgcagcattg aagaagcgct ggataacagc 1860

gcgaaagttt acacctattt tccgaccctg gcgaacaaag ttaatgcggg tgttcagggc 1920

ggtctgtttc tgatgtgggc gaacgatgtg gtggaagatt tcaccaccaa catcctgcgt 1980

aaagataccc tggataaaat cagcgatgtt agcgcgatta ttccgtatat tggtccggcg 2040

ctgaacatta gcaatagcgt gcgtcgtggc aattttaccg aagcgtttgc ggttaccggt 2100

gtgaccattc tgctggaagc gtttccggaa tttaccattc cggcgctggg tgcgtttgtg 2160

atctatagca aagtgcagga acgcaacgaa atcatcaaaa ccatcgataa ctgcctggaa 2220

cagcgtatta aacgctggaa agatagctat gaatggatga tgggcacctg gctgagccgt 2280

attatcaccc agttcaacaa catcagctac cagatgtacg atagcctgaa ctatcaggcg 2340

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aacatcaaaa gccaggttga aaacctgaaa aacagcctgg atgtgaaaat tagcgaagcg 2460

atgaataaca tcaacaaatt catccgcgaa tgcagcgtga cctacctgtt caaaaacatg 2520

ctgccgaaag tgatcgatga actgaacgaa tttgatcgca acaccaaagc gaaactgatc 2580

aacctgatcg atagccacaa cattattctg gtgggcgaag tggataaact gaaagcgaaa 2640

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ctgctgaaag atatcatcaa cgaatacttc aatctagact ag 2742

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<211> 913
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 20

Gly Ser Glu Phe Met Pro Ile Thr Ile Asn Asn Phe Asn Tyr Ser Asp
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Pro Val Asp Asn Lys Asn Ile Leu Tyr Leu Asp Thr His Leu Asn Thr
            20                  25                  30

Leu Ala Asn Glu Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn Ile Trp
        35                  40                  45

Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys
    50                  55                  60

Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr
65                  70                  75                  80

Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys
                85                  90                  95

Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr
            100                 105                 110

Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile
        115                 120                 125

Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr
    130                 135                 140

Arg Gln Gly Asn Asn Trp Val Lys Thr Gly Ser Ile Asn Pro Ser Val
145                 150                 155                 160

Ile Ile Thr Gly Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr Ser Thr
                165                 170                 175

Phe Lys Leu Thr Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe Gly Ala
            180                 185                 190

Leu Ser Ile Ile Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr Ser Asn
        195                 200                 205

Ala Thr Asn Asp Val Gly Glu Gly Arg Phe Ser Lys Ser Glu Phe Cys
    210                 215                 220

Met Asp Pro Ile Leu Ile Leu Met His Glu Leu Asn His Ala Met His
225                 230                 235                 240

Asn Leu Tyr Gly Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser Ser Val
                245                 250                 255
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Thr Ser Asn Ile Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu Tyr Ala
260 265 270

Glu Ile Tyr Ala Phe Gly Gly Pro Thr Ile Asp Leu Ile Pro Lys Ser
275 280 285

Ala Arg Lys Tyr Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg Ser Ile
290 295 300

Ala Lys Arg Leu Asn Ser Ile Thr Thr Ala Asn Pro Ser Ser Phe Asn
305 310 315 320

Lys Tyr Ile Gly Glu Tyr Lys Gln Lys Leu Ile Arg Lys Tyr Arg Phe
325 330 335

Val Val Glu Ser Ser Gly Glu Val Thr Val Asn Arg Asn Lys Phe Val
340 345 350

Glu Leu Tyr Asn Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn Tyr Ala
355 360 365

Lys Ile Tyr Asn Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn Val Tyr
370 375 380

Thr Pro Val Thr Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp Ile Gln
385 390 395 400

Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly
405 410 415

Gln Asn Leu Ser Arg Asn Pro Ala Leu Arg Lys Val Asn Pro Glu Asn
420 425 430

Met Leu Tyr Leu Phe Thr Lys Phe Cys Val Asp Gly Ile Ile Thr Ser
435 440 445

Lys Thr Lys Ser Leu Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala
450 455 460

Arg Lys Ser Ala Arg Lys Leu Ala Asn Gln Ala Leu Ala Gly Gly Gly
465 470 475 480

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu
485 490 495

Gln Cys Arg Glu Leu Leu Val Lys Asn Thr Asp Leu Pro Phe Ile Gly

500 505 510

Asp Ile Ser Asp Val Lys Thr Asp Ile Phe Leu Arg Lys Asp Ile Asn
515 520 525

Glu Glu Thr Glu Val Ile Tyr Tyr Pro Asp Asn Val Ser Val Asp Gln
530 535 540

Val Ile Leu Ser Lys Asn Thr Ser Glu His Gly Gln Leu Asp Leu Leu
545 550 555 560

Tyr Pro Ser Ile Asp Ser Glu Ser Glu Ile Leu Pro Gly Glu Asn Gln
565 570 575

Val Phe Tyr Asp Asn Arg Thr Gln Asn Val Asp Tyr Leu Asn Ser Tyr
580 585 590

Tyr Tyr Leu Glu Ser Gln Lys Leu Ser Asp Asn Val Glu Asp Phe Thr
595 600 605

Phe Thr Arg Ser Ile Glu Glu Ala Leu Asp Asn Ser Ala Lys Val Tyr
610 615 620

Thr Tyr Phe Pro Thr Leu Ala Asn Lys Val Asn Ala Gly Val Gln Gly
625 630 635 640

Gly Leu Phe Leu Met Trp Ala Asn Asp Val Val Glu Asp Phe Thr Thr
645 650 655

Asn Ile Leu Arg Lys Asp Thr Leu Asp Lys Ile Ser Asp Val Ser Ala
660 665 670

Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Ser Asn Ser Val Arg
675 680 685

Arg Gly Asn Phe Thr Glu Ala Phe Ala Val Thr Gly Val Thr Ile Leu
690 695 700

Leu Glu Ala Phe Pro Glu Phe Thr Ile Pro Ala Leu Gly Ala Phe Val
705 710 715 720

Ile Tyr Ser Lys Val Gln Glu Arg Asn Glu Ile Ile Lys Thr Ile Asp
725 730 735

Asn Cys Leu Glu Gln Arg Ile Lys Arg Trp Lys Asp Ser Tyr Glu Trp
740 745 750

Met Met Gly Thr Trp Leu Ser Arg Ile Ile Thr Gln Phe Asn Asn Ile
755 760 765

Ser Tyr Gln Met Tyr Asp Ser Leu Asn Tyr Gln Ala Gly Ala Ile Lys
770 775 780

Ala Lys Ile Asp Leu Glu Tyr Lys Lys Tyr Ser Gly Ser Asp Lys Glu
785 790 795 800

Asn Ile Lys Ser Gln Val Glu Asn Leu Lys Asn Ser Leu Asp Val Lys
805 810 815

Ile Ser Glu Ala Met Asn Asn Ile Asn Lys Phe Ile Arg Glu Cys Ser
820 825 830

Val Thr Tyr Leu Phe Lys Asn Met Leu Pro Lys Val Ile Asp Glu Leu
835 840 845

Asn Glu Phe Asp Arg Asn Thr Lys Ala Lys Leu Ile Asn Leu Ile Asp
850 855 860

Ser His Asn Ile Ile Leu Val Gly Glu Val Asp Lys Leu Lys Ala Lys
865 870 875 880

Val Asn Asn Ser Phe Gln Asn Thr Ile Pro Phe Asn Ile Phe Ser Tyr
885 890 895

Thr Asn Asn Ser Leu Leu Lys Asp Ile Ile Asn Glu Tyr Phe Asn Leu
900 905 910

Asp

<210> 21
<211> 2673
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

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ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

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actaaatctc tgatagaagg tagatacggt ggtttcatgg cgctagcggg cggtggcggt 1380

agcggcggtg gcggtagcgg cggtggcggt agcgcactag tgctgcagtg tatcaaggtt 1440

aacaactggg atttattctt cagcccgagt gaagacaact tcaccaacga cctgaacaaa 1500

ggtgaagaaa tcacctcaga tactaacatc gaagcagccg aagaaaacat ctcgctggac 1560

ctgatccagc agtactacct gacctttaat ttcgacaacg agccggaaaa catttctatc 1620

gaaaacctga gctctgatat catcggccag ctggaactga tgccgaacat cgaacgtttc 1680

ccaaacggta aaaagtacga gctggacaaa tataccatgt tccactacct gcgcgcgcag 1740

gaatttgaac acggcaaatc ccgtatcgca ctgactaact ccgttaacga agctctgctc 1800

aacccgtccc gtgtatacac cttcttctct agcgactacg tgaaaaaggt caacaaagcg 1860

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gaaaaaaaca acatcaactt caacatcgac gatctgtcct ctaaactgaa cgaatccatc 2400

aacaaagcta tgatcaacat caacaagttc ctgaaccagt gctctgtaag ctatctgatg 2460

aactccatga tcccgtacgg tgttaaacgt ctggaggact tcgatgcgtc tctgaaagac 2520

gccctgctga aatacattta cgacaaccgt ggcactctga tcggtcaggt tgatcgtctg 2580

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<223> Synthetic

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20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

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Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350
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Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Tyr Gly Gly Phe Met Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly
    450                 455                 460

Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val
465                 470                 475                 480

Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn
                485                 490                 495

Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala
            500                 505                 510

Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr
        515                 520                 525

Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser
    530                 535                 540

Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe
545                 550                 555                 560

Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr
                565                 570                 575

Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr
            580                 585                 590

Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe
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595 600 605

Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala
610 615 620

Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu
625 630 635 640

Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile
645 650 655

Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys
660 665 670

Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu
675 680 685

Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu
690 695 700

Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn
705 710 715 720

Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile
725 730 735

Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg
740 745 750

Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala
755 760 765

Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn
770 775 780

Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile
785 790 795 800

Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val
805 810 815

Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu
820 825 830

Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp
835 840 845

Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val
850 855 860

Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val
865 870 875 880

Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
885 890

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<212> DNA
<213> Artificial Sequence

<220>
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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

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cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

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ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

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gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

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ctgcagtgta tcaaggttaa caactgggat ttattcttca gcccgagtga agacaacttc 1560

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aaaaaggtca acaaagcgac tgaagctgca atgttcttgg gttgggttga acagcttgtt 1980

tatgatttta ccgacgagac gtccgaagta tctactaccg acaaaattgc ggatatcact 2040

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gatgcgtctc tgaaagacgc cctgctgaaa tacatttacg acaaccgtgg cactctgatc 2640

ggtcaggttg atcgtctgaa ggacaaagtg aacaatacct tatcgaccga catcctttt 2700

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<213> Artificial Sequence

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<223> Synthetic

<400> 24

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            20                  25                  30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
        35                  40                  45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
    50                  55                  60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65                  70                  75                  80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
                85                  90                  95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
            100                 105                 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
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225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
435 440 445

Tyr Gly Gly Phe Met Thr Ser Glu Lys Ser Gln Thr Pro Leu Val Thr
450 455 460

Leu Phe Lys Asn Ala Ile Ile Lys Asn Ala Tyr Lys Lys Gly Glu Ala
465 470 475 480

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Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                485                 490                 495

Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe
            500                 505                 510

Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu
        515                 520                 525

Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser
    530                 535                 540

Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu
545                 550                 555                 560

Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln
                565                 570                 575

Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr
            580                 585                 590

Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe
        595                 600                 605

Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala
    610                 615                 620

Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val
625                 630                 635                 640

Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val
                645                 650                 655

Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr
            660                 665                 670

Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro
        675                 680                 685

Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala
    690                 695                 700

Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile
705                 710                 715                 720
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Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn
725 730 735

Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn
740 745 750

Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala
755 760 765

Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala
770 775 780

Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr
785 790 795 800

Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp
805 810 815

Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn
820 825 830

Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser
835 840 845

Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu
850 855 860

Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile
865 870 875 880

Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr
885 890 895

Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu
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Ser Thr Leu Asp
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<211> 2709
<212> DNA
<213> Artificial Sequence

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<223> Synthetic

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

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ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

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aaaattgcgg atatcactat catcatcccg tacatcggtc cggctctgaa cattggcaac 2040

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<212> PRT
<213> Artificial Sequence

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<223> Synthetic

<400> 26

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

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Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
                85                  90                  95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
            100                 105                 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320
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Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
                485                 490                 495

Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
            500                 505                 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
        515                 520                 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
    530                 535                 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
545                 550                 555                 560
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Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
                565                 570                 575

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
            580                 585                 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
        595                 600                 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
    610                 615                 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
625                 630                 635                 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
                645                 650                 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
            660                 665                 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val
        675                 680                 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
    690                 695                 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705                 710                 715                 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
                725                 730                 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
            740                 745                 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
        755                 760                 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
    770                 775                 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785                 790                 795                 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
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805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Asp
900

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<211> 2691
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<213> Artificial Sequence

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<223> Synthetic

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

ttcactggtc tgttcgagtt ttacaagctg ctgtgcgtcg acggcatcat tacctccaaa 1320

actaaatctc tgatagaagg tagatttggc ggtttcacgg gcgcacgcaa atcagcggcg 1380

ctagcgggcg gtggcggtag cggcggtggc ggtagcggcg gtggcggtag cgcactagtg 1440

ctgcagtgta tcaaggttaa caactgggat ttattcttca gcccgagtga agacaacttc 1500

accaacgacc tgaacaaagg tgaagaaatc acctcagata ctaacatcga agcagccgaa 1560

gaaaacatct cgctggacct gatccagcag tactacctga cctttaattt cgacaacgag 1620

ccggaaaaca tttctatcga aaacctgagc tctgatatca tcggccagct ggaactgatg 1680

ccgaacatcg aacgtttccc aaacggtaaa aagtacgagc tggacaaata taccatgttc 1740

cactacctgc gcgcgcagga atttgaacac ggcaaatccc gtatcgcact gactaactcc 1800

gttaacgaag ctctgctcaa cccgtcccgt gtatacacct tcttctctag cgactacgtg 1860

aaaaaggtca acaaagcgac tgaagctgca atgttcttgg gttgggttga acagcttgtt 1920

tatgatttta ccgacgagac gtccgaagta tctactaccg acaaaattgc ggatatcact 1980

atcatcatcc cgtacatcgg tccggctctg aacattggca acatgctgta caaagacgac 2040

ttcgttggcg cactgatctt ctccggtgcg gtgatcctgc tggagttcat cccggaaatc 2100

gccatcccgg tactgggcac ctttgctctg gtttcttaca ttgcaaacaa ggttctgact 2160

gtacaaacca tcgacaacgc gctgagcaaa cgtaacgaaa aatgggatga agtttacaaa 2220

tatatcgtga ccaactggct ggctaaggtt aatactcaga tcgacctcat ccgcaaaaaa 2280

atgaaagaag cactggaaaa ccaggcggaa gctaccaagg caatcattaa ctaccagtac 2340

aaccagtaca ccgaggaaga aaaaaacaac atcaacttca acatcgacga tctgtcctct 2400

aaactgaacg aatccatcaa caaagctatg atcaacatca acaagttcct gaaccagtgc 2460

tctgtaagct atctgatgaa ctccatgatc ccgtacggtg ttaaacgtct ggaggacttc 2520

gatgcgtctc tgaaagacgc cctgctgaaa tacatttacg acaaccgtgg cactctgatc 2580

ggtcaggttg atcgtctgaa ggacaaagtg aacaatacct tatcgaccga catccctttt 2640

cagctcagta aatatgtcga taaccaacgc cttttgtcca ctctagacta g 2691

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<211> 896
<212> PRT
<213> Artificial Sequence

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<223> Synthetic

<400> 28

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

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Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430
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Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
435 440 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Ala Leu Ala Gly Gly
450 455 460

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val
465 470 475 480

Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser
485 490 495

Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser
500 505 510

Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile
515 520 525

Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile
530 535 540

Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met
545 550 555 560

Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys
565 570 575

Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys
580 585 590

Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro
595 600 605

Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn
610 615 620

Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val
625 630 635 640

Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile
645 650 655

Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile
660 665 670

Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser
675 680 685

Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val
690 695 700

Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr
705 710 715 720

Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp
725 730 735

Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr
740 745 750

Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln
755 760 765

Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr
770 775 780

Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser
785 790 795 800

Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe
805 810 815

Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr
820 825 830

Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu
835 840 845

Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp
850 855 860

Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe
865 870 875 880

Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
885 890 895

<210> 29
<211> 2691
<212> DNA
<213> Artificial Sequence

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<223> Synthetic

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

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accaacgacc tgaacaaagg tgaagaaatc acctcagata ctaacatcga agcagccgaa 1560

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ccggaaaaca tttctatcga aaacctgagc tctgatatca tcggccagct ggaactgatg 1680

ccgaacatcg aacgtttccc aaacggtaaa aagtacgagc tggacaaata taccatgttc 1740

cactacctgc gcgcgcagga atttgaacac ggcaaatccc gtatcgcact gactaactcc 1800

gttaacgaag ctctgctcaa cccgtcccgt gtatacacct tcttctctag cgactacgtg 1860

aaaaaggtca acaaagcgac tgaagctgca atgttcttgg gttgggttga acagcttgtt 1920

tatgatttta ccgacgagac gtccgaagta tctactaccg acaaaattgc ggatatcact 1980

atcatcatcc cgtacatcgg tccggctctg aacattggca acatgctgta caaagacgac 2040

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gccatcccgg tactgggcac ctttgctctg gtttcttaca ttgcaaacaa ggttctgact 2160

gtacaaacca tcgacaacgc gctgagcaaa cgtaacgaaa aatgggatga agtttacaaa 2220

tatatcgtga ccaactggct ggctaaggtt aatactcaga tcgacctcat ccgcaaaaaa 2280

atgaaagaag cactggaaaa ccaggcggaa gctaccaagg caatcattaa ctaccagtac 2340

aaccagtaca ccgaggaaga aaaaaacaac atcaacttca acatcgacga tctgtcctct 2400

aaactgaacg aatccatcaa caaagctatg atcaacatca acaagttcct gaaccagtgc 2460

tctgtaagct atctgatgaa ctccatgatc ccgtacggtg ttaaacgtct ggaggacttc 2520

gatgcgtctc tgaaagacgc cctgctgaaa tacatttacg acaaccgtgg cactctgatc 2580

ggtcaggttg atcgtctgaa ggacaaagtg aacaatacct tatcgaccga catccctttt 2640

cagctcagta aatatgtcga taaccaacgc cttttgtcca ctctagacta g 2691

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<211> 896
<212> PRT
<213> Artificial Sequence

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<400> 30

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu

65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305 310 315 320

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Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Tyr Ala Ala Leu Ala Gly Gly
    450                 455                 460

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val
465                 470                 475                 480

Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser
                485                 490                 495

Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser
            500                 505                 510

Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile
        515                 520                 525

Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile
    530                 535                 540

Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met
545                 550                 555                 560
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Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys
                565                 570                 575

Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys
            580                 585                 590

Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro
        595                 600                 605

Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn
    610                 615                 620

Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val
625                 630                 635                 640

Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile
                645                 650                 655

Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile
            660                 665                 670

Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser
        675                 680                 685

Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val
    690                 695                 700

Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr
705                 710                 715                 720

Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp
                725                 730                 735

Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr
            740                 745                 750

Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln
        755                 760                 765

Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr
    770                 775                 780

Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser
785                 790                 795                 800
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Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe
805 810 815

Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr
820 825 830

Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu
835 840 845

Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp
850 855 860

Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe
865 870 875 880

Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
885 890 895

<210> 31
<211> 2691
<212> DNA
<213> Artificial Sequence

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<223> Synthetic

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

ttcactggtc tgttcgagtt ttacaagctg ctgtgcgtcg acggcatcat tacctccaaa 1320

actaaatctc tgatagaagg tagatttggc ggtttcacgg gcgcacgcaa atcatatgcg 1380

ctagcgggcg gtggcggtag cggcggtggc ggtagcggcg gtggcggtag cgcactagtg 1440

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accaacgacc tgaacaaagg tgaagaaatc acctcagata ctaacatcga agcagccgaa 1560

gaaaacatct cgctggacct gatccagcag tactacctga cctttaattt cgacaacgag 1620

ccggaaaaca tttctatcga aaacctgagc tctgatatca tcggccagct ggaactgatg 1680

ccgaacatcg aacgtttccc aaacggtaaa aagtacgagc tggacaaata taccatgttc 1740

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atcatcatcc cgtacatcgg tccggctctg aacattggca acatgctgta caaagacgac 2040

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gtacaaacca tcgacaacgc gctgagcaaa cgtaacgaaa aatgggatga agtttacaaa 2220

tatatcgtga ccaactggct ggctaaggtt aatactcaga tcgacctcat ccgcaaaaaa 2280

atgaaagaag cactggaaaa ccaggcggaa gctaccaagg caatcattaa ctaccagtac 2340

aaccagtaca ccgaggaaga aaaaaacaac atcaacttca acatcgacga tctgtcctct 2400

aaactgaacg aatccatcaa caaagctatg atcaacatca acaagttcct gaaccagtgc 2460

tctgtaagct atctgatgaa ctccatgatc ccgtacggtg ttaaacgtct ggaggacttc 2520

gatgcgtctc tgaaagacgc cctgctgaaa tacatttacg acaaccgtgg cactctgatc 2580

ggtcaggttg atcgtctgaa ggacaaagtg aacaatacct tatcgaccga catcccttt 2640

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<211> 896
<212> PRT
<213> Artificial Sequence

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<223> Synthetic

<400> 32

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro

195 200 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
210 215 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225 230 235 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
245 250 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
260 265 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
275 280 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
290 295 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305 310 315 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
325 330 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
340 345 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
355 360 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
370 375 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
435 440 445

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Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Tyr Ala Leu Ala Gly Gly
    450                 455                 460

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val
465                 470                 475                 480

Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser
                485                 490                 495

Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser
            500                 505                 510

Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile
        515                 520                 525

Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile
    530                 535                 540

Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met
545                 550                 555                 560

Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys
                565                 570                 575

Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys
            580                 585                 590

Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro
        595                 600                 605

Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn
    610                 615                 620

Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val
625                 630                 635                 640

Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile
                645                 650                 655

Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile
            660                 665                 670

Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser
        675                 680                 685
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Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val
    690                 695                 700

Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr
705                 710                 715                 720

Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp
                725                 730                 735

Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr
            740                 745                 750

Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln
        755                 760                 765

Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr
    770                 775                 780

Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser
785                 790                 795                 800

Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe
                805                 810                 815

Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr
            820                 825                 830

Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu
        835                 840                 845

Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp
    850                 855                 860

Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe
865                 870                 875                 880

Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
                885                 890                 895
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<211> 2709
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

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actaaatctc tgatagaagg tagatttggc ggtttcacgg gcgcacgcaa atcagcgcgt 1380

aaatatgcta accaggcgct agcgggcggt ggcggtagcg gcggtggcgg tagcggcggt 1440

ggcggtagcg cactagtgct gcagtgtatc aaggttaaca actgggattt attcttcagc 1500

ccgagtgaag acaacttcac caacgacctg aacaaaggtg aagaaatcac ctcagatact 1560

aacatcgaag cagccgaaga aaacatctcg ctggacctga tccagcagta ctacctgacc 1620

tttaatttcg acaacgagcc ggaaaacatt tctatcgaaa acctgagctc tgatatcatc 1680

ggccagctgg aactgatgcc gaacatcgaa cgtttcccaa acggtaaaaa gtacgagctg 1740

gacaaatata ccatgttcca ctacctgcgc gcgcaggaat ttgaacacgg caaatcccgt 1800

atcgcactga ctaactccgt taacgaagct ctgctcaacc cgtcccgtgt atacaccttc 1860

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tgggttgaac agcttgttta tgattttacc gacgagacgt ccgaagtatc tactaccgac 1980

aaaattgcgg atatcactat catcatcccg tacatcggtc cggctctgaa cattggcaac 2040

atgctgtaca aagacgactt cgttggcgca ctgatcttct ccggtgcggt gatcctgctg 2100

gagttcatcc cggaaatcgc catcccggta ctgggcacct ttgctctggt ttcttacatt 2160

gcaaacaagg ttctgactgt acaaaccatc gacaacgcgc tgagcaaacg taacgaaaaa 2220

tgggatgaag tttacaaata tatcgtgacc aactggctgg ctaaggttaa tactcagatc 2280

gacctcatcc gcaaaaaaat gaaagaagca ctggaaaacc aggcggaagc taccaaggca 2340

atcattaact accagtacaa ccagtacacc gaggaagaaa aaaacaacat caacttcaac 2400

atcgacgatc tgtcctctaa actgaacgaa tccatcaaca aagctatgat caacatcaac 2460

aagttcctga accagtgctc tgtaagctat ctgatgaact ccatgatccc gtacggtgtt 2520

aaacgtctgg aggacttcga tgcgtctctg aaagacgccc tgctgaaata catttacgac 2580

aaccgtggca ctctgatcgg tcaggttgat cgtctgaagg acaaagtgaa caatacctta 2640

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<212> PRT
<213> Artificial Sequence

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<223> Synthetic

<400> 34

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

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Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
                85                  90                  95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
            100                 105                 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320
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Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Tyr Ala Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
                485                 490                 495

Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
            500                 505                 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
        515                 520                 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
    530                 535                 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
545                 550                 555                 560
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Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
                565                 570                 575

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
            580                 585                 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
        595                 600                 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
    610                 615                 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
625                 630                 635                 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
                645                 650                 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
            660                 665                 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val
        675                 680                 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
    690                 695                 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705                 710                 715                 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
                725                 730                 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
            740                 745                 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
        755                 760                 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
    770                 775                 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785                 790                 795                 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
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805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Asp
900

<210> 35
<211> 2697
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

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aacgagccgg aaaacatttc tatcgaaaac ctgagctctg atatcatcgg ccagctggaa 1680

ctgatgccga acatcgaacg tttcccaaac ggtaaaaagt acgagctgga caaatatacc 1740

atgttccact acctgcgcgc gcaggaattt gaacacggca aatcccgtat cgcactgact 1800

aactccgtta acgaagctct gctcaacccg tcccgtgtat acaccttctt ctctagcgac 1860

tacgtgaaaa aggtcaacaa agcgactgaa gctgcaatgt tcttgggttg ggttgaacag 1920

cttgtttatg attttaccga cgagacgtcc gaagtatcta ctaccgacaa aattgcggat 1980

atcactatca tcatcccgta catcggtccg gctctgaaca ttggcaacat gctgtacaaa 2040

gacgacttcg ttggcgcact gatcttctcc ggtgcggtga tcctgctgga gttcatcccg 2100

gaaatcgcca tcccggtact gggcaccttt gctctggttt cttacattgc aaacaaggtt 2160

ctgactgtac aaaccatcga caacgcgctg agcaaacgta acgaaaaatg ggatgaagtt 2220

tacaaatata tcgtgaccaa ctggctggct aaggttaata ctcagatcga cctcatccgc 2280

aaaaaaatga aagaagcact ggaaaaccag gcggaagcta ccaaggcaat cattaactac 2340

cagtacaacc agtacaccga ggaagaaaaa aacaacatca acttcaacat cgacgatctg 2400

tcctctaaac tgaacgaatc catcaacaaa gctatgatca acatcaacaa gttcctgaac 2460

cagtgctctg taagctatct gatgaactcc atgatcccgt acggtgttaa acgtctggag 2520

gacttcgatg cgtctctgaa agacgccctg ctgaaataca tttacgacaa ccgtggcact 2580

ctgatcggtc aggttgatcg tctgaaggac aaagtgaaca ataccttatc gaccgacatc 2640

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<210> 36
<211> 898
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 36

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
1 5 10 15

Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145 150 155 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
165 170 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
180 185 190

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Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430
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Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Ala Leu Ala
    450                 455                 460

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
465                 470                 475                 480

Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser
                485                 490                 495

Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile
            500                 505                 510

Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp
        515                 520                 525

Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu
    530                 535                 540

Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu
545                 550                 555                 560

Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu
                565                 570                 575

Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His
            580                 585                 590

Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu
        595                 600                 605

Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys
    610                 615                 620

Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln
625                 630                 635                 640

Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp
                645                 650                 655

Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu
            660                 665                 670
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Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile
        675                 680                 685

Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile
    690                 695                 700

Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val
705                 710                 715                 720

Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys
                725                 730                 735

Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val
            740                 745                 750

Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu
        755                 760                 765

Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln
    770                 775                 780

Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu
785                 790                 795                 800

Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn
                805                 810                 815

Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile
            820                 825                 830

Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp
        835                 840                 845

Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln
    850                 855                 860

Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile
865                 870                 875                 880

Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr
                885                 890                 895

Leu Asp
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<210> 37

<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 37
tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaat tagctaacca g 51

<210> 38
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 38

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
1 5 10 15

Gln

<210> 39
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 39
tttggcggtt tcacgggcgc acgcaaatca gcg 33

<210> 40
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 40

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala
1 5 10

<210> 41
<211> 33
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 41
tttggcggtt tcacgggcgc acgcaaatat gcg 33

<210> 42
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 42

Phe Gly Gly Phe Thr Gly Ala Arg Lys Tyr Ala
1 5 10

<210> 43
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 43
tttggcggtt tcacgggcgc acgcaaatca tat 33

<210> 44
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 44

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Tyr
1 5 10

<210> 45
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 45
tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaat atgctaacca g 51

<210> 46
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 46

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Tyr Ala Asn
1 5 10 15

Gln

<210> 47
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 47
tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaa 39

<210> 48
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 48

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys
1 5 10

<210> 49
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 49
tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaac gcaaaaacca g 51

<210> 50
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 50

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
1 5 10 15

Gln

<210> 51
<211> 2736
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 51
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gctaaccaga ctagtggcgg tgggggtagt ggcggtggcg gttcgggcgg gggtgggagc 120

cctaggggat ccatggagtt cgttaacaaa cagttcaact ataaagaccc agttaacggt 180

gttgacattg cttacatcaa aatcccgaac gctggccaga tgcagccggt aaaggcattc 240

aaaatccaca acaaaatctg ggttatcccg gaacgtgata cctttactaa cccggaagaa 300

ggtgacctga acccgccacc ggaagcgaaa caggtgccgg tatcttacta tgactccacc 360

tacctgtcta ccgataacga aaaggacaac tacctgaaag gtgttactaa actgttcgag 420

cgtatttact ccaccgacct gggccgtatg ctgctgacta gcatcgttcg cggtatcccg 480

ttctggggcg gttctaccat cgataccgaa ctgaaagtaa tcgacactaa ctgcatcaac 540

gttattcagc cggacggttc ctatcgttcc gaagaactga acctggtgat catcggcccg 600

tctgctgata tcatccagtt cgagtgtaag agctttggtc acgaagttct gaacctcacc 660

cgtaacggct acggttccac tcagtacatc cgtttctctc cggacttcac cttcggtttt 720

gaagaatccc tggaagtaga cacgaaccca ctgctgggcg ctggtaaatt cgcaactgat 780

cctgcggtta ccctggctca cgaactgatt catgcaggcc accgcctgta cggtatcgcc 840

atcaatccga accgtgtctt caaagttaac accaacgcgt attacgagat gtccggtctg 900

gaagttagct tcgaagaact gcgtactttt ggcggtcacg acgctaaatt catcgactct 960

ctgcaagaaa acgagttccg tctgtactac tataacaagt tcaaagatat cgcatccacc 1020

ctgaacaaag cgaaatccat cgtgggtacc actgcttctc tccagtacat gaagaacgtt 1080

tttaaagaaa aatacctgct cagcgaagac acctccggca aattctctgt agacaagttg 1140

aaattcgata aactttacaa aatgctgact gaaatttaca ccgaagacaa cttcgttaag 1200

ttctttaaag ttctgaaccg caaaacctat ctgaacttcg acaaggcagt attcaaaatc 1260

aacatcgtgc cgaaagttaa ctacactatc tacgatggtt tcaacctgcg taacaccaac 1320

ctggctgcta attttaacgg ccagaacacg gaaatcaaca acatgaactt cacaaaactg 1380

aaaaacttca ctggtctgtt cgagttttac aagctgctgt gcgtcgacgg catcattacc 1440

tccaaaacta aatctctgat agaaggtaga aacaaagcgc tgaacctgca gtgtatcaag 1500

gttaacaact gggatttatt cttcagcccg agtgaagaca acttcaccaa cgacctgaac 1560

aaaggtgaag aaatcacctc agatactaac atcgaagcag ccgaagaaaa catctcgctg 1620

gacctgatcc agcagtacta cctgaccttt aatttcgaca acgagccgga aaacatttct 1680

atcgaaaacc tgagctctga tatcatcggc cagctggaac tgatgccgaa catcgaacgt 1740

ttcccaaacg gtaaaaagta cgagctggac aaatatacca tgttccacta cctgcgcgcg 1800

caggaatttg aacacggcaa atcccgtatc gcactgacta actccgttaa cgaagctctg 1860

ctcaacccgt cccgtgtata caccttcttc tctagcgact acgtgaaaaa ggtcaacaaa 1920

gcgactgaag ctgcaatgtt cttgggttgg gttgaacagc ttgtttatga ttttaccgac 1980

gagacgtccg aagtatctac taccgacaaa attgcggata tcactatcat catcccgtac 2040

atcggtccgg ctctgaacat tggcaacatg ctgtacaaag acgacttcgt tggcgcactg 2100

atcttctccg gtgcggtgat cctgctggag ttcatcccgg aaatcgccat cccggtactg 2160

ggcacctttg ctctggtttc ttacattgca aacaaggttc tgactgtaca aaccatcgac 2220

aacgcgctga gcaaacgtaa cgaaaaatgg gatgaagttt acaaatatat cgtgaccaac 2280

tggctggcta aggttaatac tcagatcgac ctcatccgca aaaaaatgaa agaagcactg 2340

gaaaaccagg cggaagctac caaggcaatc attaactacc agtacaacca gtacaccgag 2400

gaagaaaaaa acaacatcaa cttcaacatc gacgatctgt cctctaaact gaacgaatcc 2460

atcaacaaag ctatgatcaa catcaacaag ttcctgaacc agtgctctgt aagctatctg 2520

atgaactcca tgatcccgta cggtgttaaa cgtctggagg acttcgatgc gtctctgaaa 2580

gacgccctgc tgaaatacat ttacgacaac cgtggcactc tgatcggtca ggttgatcgt 2640

ctgaaggaca aagtgaacaa taccttatcg accgacatcc cttttcagct cagtaaatat 2700

gtcgataacc aacgcctttt gtccactcta gactag 2736

<210> 52
<211> 911
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 52

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Leu Gly Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser
1               5                  10                  15

Ala Arg Lys Leu Ala Asn Gln Thr Ser Gly Gly Gly Gly Ser Gly Gly
            20                  25                  30

Gly Gly Ser Gly Gly Gly Gly Ser Pro Arg Gly Ser Met Glu Phe Val
        35                  40                  45

Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val Asn Gly Val Asp Ile Ala
    50                  55                  60

Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met Gln Pro Val Lys Ala Phe
65                  70                  75                  80

Lys Ile His Asn Lys Ile Trp Val Ile Pro Glu Arg Asp Thr Phe Thr
                85                  90                  95

Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro Pro Glu Ala Lys Gln Val
            100                 105                 110

Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu Ser Thr Asp Asn Glu Lys
        115                 120                 125

Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu Phe Glu Arg Ile Tyr Ser
    130                 135                 140

Thr Asp Leu Gly Arg Met Leu Leu Thr Ser Ile Val Arg Gly Ile Pro
145                 150                 155                 160

Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu Leu Lys Val Ile Asp Thr
                165                 170                 175

Asn Cys Ile Asn Val Ile Gln Pro Asp Gly Ser Tyr Arg Ser Glu Glu
            180                 185                 190

Leu Asn Leu Val Ile Ile Gly Pro Ser Ala Asp Ile Ile Gln Phe Glu
        195                 200                 205

Cys Lys Ser Phe Gly His Glu Val Leu Asn Leu Thr Arg Asn Gly Tyr
    210                 215                 220

Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro Asp Phe Thr Phe Gly Phe
225                 230                 235                 240

Glu Glu Ser Leu Glu Val Asp Thr Asn Pro Leu Leu Gly Ala Gly Lys
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245 250 255

Phe Ala Thr Asp Pro Ala Val Thr Leu Ala His Glu Leu Ile His Ala
260 265 270

Gly His Arg Leu Tyr Gly Ile Ala Ile Asn Pro Asn Arg Val Phe Lys
275 280 285

Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser Gly Leu Glu Val Ser Phe
290 295 300

Glu Glu Leu Arg Thr Phe Gly Gly His Asp Ala Lys Phe Ile Asp Ser
305 310 315 320

Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr Tyr Asn Lys Phe Lys Asp
325 330 335

Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser Ile Val Gly Thr Thr Ala
340 345 350

Ser Leu Gln Tyr Met Lys Asn Val Phe Lys Glu Lys Tyr Leu Leu Ser
355 360 365

Glu Asp Thr Ser Gly Lys Phe Ser Val Asp Lys Leu Lys Phe Asp Lys
370 375 380

Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr Glu Asp Asn Phe Val Lys
385 390 395 400

Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr Leu Asn Phe Asp Lys Ala
405 410 415

Val Phe Lys Ile Asn Ile Val Pro Lys Val Asn Tyr Thr Ile Tyr Asp
420 425 430

Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala Ala Asn Phe Asn Gly Gln
435 440 445

Asn Thr Glu Ile Asn Asn Met Asn Phe Thr Lys Leu Lys Asn Phe Thr
450 455 460

Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys Val Asp Gly Ile Ile Thr
465 470 475 480

Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg Asn Lys Ala Leu Asn Leu
485 490 495

```
Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu
            500                 505                 510

Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp
        515                 520                 525

Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln
    530                 535                 540

Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser
545                 550                 555                 560

Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro
                565                 570                 575

Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr
            580                 585                 590

Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser
        595                 600                 605

Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser
    610                 615                 620

Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys
625                 630                 635                 640

Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr
                645                 650                 655

Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala
            660                 665                 670

Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly
        675                 680                 685

Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly
    690                 695                 700

Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu
705                 710                 715                 720

Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val
                725                 730                 735
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Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu
740 745 750

Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln
755 760 765

Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala
770 775 780

Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu
785 790 795 800

Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys
805 810 815

Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu
820 825 830

Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly
835 840 845

Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu
850 855 860

Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg
865 870 875 880

Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln
885 890 895

Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
900 905 910

<210> 53
<211> 177
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 53
ggatccacgc acgtcgacgg catcattacc tccaaaacta aatctctgat agaaggtaga 60

tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaat tagctaacca ggcgctagcg 120

ggtggtggtg gttctgcact agtgctgcag acgcacggtc tagaatgata aaagctt 177

<210> 54
<211> 192
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 54
ggatccacgc acgtcgacgg catcattacc tccaaaacta aatctctgat agaaggtaga 60

tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaat tagctaacca ggcgctagcg 120

ggtggtggtg gttctggtgg tggtggttct gcactagtgc tgcagacgca cggtctagaa 180

tgataaaagc tt 192

<210> 55
<211> 222
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 55
ggatccacgc acgtcgacgg catcattacc tccaaaacta aatctctgat agaaggtaga 60

tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaat tagctaacca ggcgctagcg 120

ggtggtggtg gttctggtgg tggtggttct ggtggtggtg gttctggtgg tggtggttct 180

gcactagtgc tgcagacgca cggtctagaa tgataaaagc tt 222

<210> 56
<211> 237
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 56
ggatccacgc acgtcgacgg catcattacc tccaaaacta aatctctgat agaaggtaga 60

tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaat tagctaacca ggcgctagcg 120

ggtggtggtg gttctggtgg tggtggttct ggtggtggtg gttctggtgg tggtggttct 180

ggtggtggtg gttctgcact agtgctgcag acgcacggtc tagaatgata aaagctt 237

<210> 57
<211> 228
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 57
ggatccacgc acgtcgacgg catcattacc tccaaaacta aatctctgat agaaggtaga 60

tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaat tagctaacca ggcgctagcg 120

gctgaagctg ctgctaaaga agctgctgct aaagaagctg ctgctaaagc tggtggcggt 180

ggttccgcac tagtgctgca gacgcacggt ctagaatgat aaaagctt 228

<210> 58
<211> 2694
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 58
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attgcttaca tcaaaatccc gaacgctggc cagatgcagc cggtaaaggc attcaaaatc 120

cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

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ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
        35                  40                  45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
    50                  55                  60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65                  70                  75                  80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
                85                  90                  95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
            100                 105                 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255
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Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu
465                 470                 475                 480

Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro
                485                 490                 495
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Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr
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Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu
        515                 520                 525

Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn
    530                 535                 540

Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu
545                 550                 555                 560

Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp
                565                 570                 575

Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly
            580                 585                 590

Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn
        595                 600                 605

Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val
    610                 615                 620

Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu
625                 630                 635                 640

Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys
                645                 650                 655

Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn
            660                 665                 670

Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe
        675                 680                 685

Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro
    690                 695                 700

Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu
705                 710                 715                 720

Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp
                725                 730                 735
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Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn
740 745 750

Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn
755 760 765

Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr
770 775 780

Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser
785 790 795 800

Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys
805 810 815

Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro
820 825 830

Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala
835 840 845

Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val
850 855 860

Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro
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Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu
885 890 895

Asp

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

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Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350
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Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
            405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
        420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys
            485                 490                 495

Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr
        500                 505                 510

Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu
        515                 520                 525

Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu
    530                 535                 540

Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu
545                 550                 555                 560

Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg
            565                 570                 575

Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His
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Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu
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595 600 605

Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr
610 615 620

Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala
625 630 635 640

Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp
645 650 655

Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile
660 665 670

Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr
675 680 685

Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu
690 695 700

Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala
705 710 715 720

Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp
725 730 735

Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr
740 745 750

Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile
755 760 765

Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys
770 775 780

Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn
785 790 795 800

Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser
805 810 815

Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser
820 825 830

Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu
835 840 845

Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr
850 855 860

Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys
865 870 875 880

Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr
885 890 895

Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
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gcaaacaagg ttctgactgt acaaaccatc gacaacgcgc tgagcaaacg taacgaaaaa 2220

tgggatgaag tttacaaata tatcgtgacc aactggctgg ctaaggttaa tactcagatc 2280

gacctcatcc gcaaaaaaat gaaagaagca ctggaaaacc aggcggaagc taccaaggca 2340

atcattaact accagtacaa ccagtacacc gaggaagaaa aaaacaacat caacttcaac 2400

atcgacgatc tgtcctctaa actgaacgaa tccatcaaca aagctatgat caacatcaac 2460

aagttcctga accagtgctc tgtaagctat ctgatgaact ccatgatccc gtacggtgtt 2520

aaacgtctgg aggacttcga tgcgtctctg aaagacgccc tgctgaaata catttacgac 2580

aaccgtggca ctctgatcgg tcaggttgat cgtctgaagg acaaagtgaa caatacctta 2640

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ctagactag 2709

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<211> 902
<212> PRT
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<223> Synthetic

<400> 64

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

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Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380
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Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Asp Asp Asp Asp Lys
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
                485                 490                 495

Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
            500                 505                 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
        515                 520                 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
    530                 535                 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
545                 550                 555                 560

Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
                565                 570                 575

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
            580                 585                 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
        595                 600                 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
    610                 615                 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
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625 630 635 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
645 650 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
660 665 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val
675 680 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
690 695 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705 710 715 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
725 730 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
740 745 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
755 760 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
770 775 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785 790 795 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Asp
900

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<211> 207
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 65
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tttggcggtt tcacgggcgc acgcaaatca gcgcgtaaac gtaagaacca ggcgctagcg 120

ggcggtggcg gtagcggcgg tggcggtagc ggcggtggcg gtagcgcact agtgctgcag 180

acgcacggtc tagaatgata aaagctt 207

<210> 66
<211> 2742
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 66
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tttcgtatca ccggcaacat ttgggttatt ccggatcgtt ttagccgtaa cagcaacccg 180

aatctgaata aaccgccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat 240

ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc 300

atcaacagcc gtgaaattgg cgaagaactg atctatcgcc tgagcaccga tattccgttt 360

ccgggcaaca acaacacccc gatcaacacc tttgatttcg atgtggattt caacagcgtt 420

gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcgtg 480

attattaccg gtccgcgcga aaacattatt gatccggaaa ccagcacctt taaactgacc 540

aacaacacct ttgcggcgca ggaaggtttt ggcgcgctga gcattattag cattagcccg 600

cgctttatgc tgacctatag caacgcgacc aacgatgttg gtgaaggccg tttcagcaaa 660

agcgaatttt gcatggaccc gatcctgatc ctgatgcatg aactgaacca tgcgatgcat 720

aacctgtatg gcatcgcgat tccgaacgat cagaccatta gcagcgtgac cagcaacatc 780

ttttacagcc agtacaacgt gaaactggaa tatgcggaaa tctatgcgtt tggcggtccg 840

accattgatc tgattccgaa aagcgcgcgc aaatacttcg aagaaaaagc gctggattac 900

tatcgcagca ttgcgaaacg tctgaacagc attaccaccg cgaatccgag cagcttcaac 960

aaatatatcg gcgaatataa acagaaactg atccgcaaat atcgctttgt ggtggaaagc 1020

agcggcgaag ttaccgttaa ccgcaataaa ttcgtggaac tgtacaacga actgacccag 1080

atcttcaccg aatttaacta tgcgaaaatc tataacgtgc agaaccgtaa aatctacctg 1140

agcaacgtgt ataccccggt gaccgcgaat attctggatg ataacgtgta cgatatccag 1200

aacggcttta acatcccgaa aagcaacctg aacgttctgt ttatgggcca gaacctgagc 1260

cgtaatccgg cgctgcgtaa agtgaacccg gaaaacatgc tgtacctgtt caccaaattt 1320

tgcgtcgacg gcatcattac ctccaaaact aaatctctga tagaaggtag atttggcggt 1380

ttcacgggcg cacgcaaatc agcgcgtaaa cgtaagaacc aggcgctagc gggcggtggc 1440

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atcttcctgc gcaaagatat caacgaagaa accgaagtga tctactaccc ggataacgtg 1620

agcgttgatc aggtgatcct gagcaaaaac accagcgaac atggtcagct ggatctgctg 1680

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gcgaaagttt acacctattt tccgaccctg gcgaacaaag ttaatgcggg tgttcagggc 1920

ggtctgtttc tgatgtgggc gaacgatgtg gtggaagatt tcaccaccaa catcctgcgt 1980

aaagataccc tggataaaat cagcgatgtt agcgcgatta ttccgtatat tggtccggcg 2040

ctgaacatta gcaatagcgt gcgtcgtggc aattttaccg aagcgtttgc ggttaccggt 2100

gtgaccattc tgctggaagc gtttccggaa tttaccattc cggcgctggg tgcgtttgtg 2160

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cagcgtatta aacgctggaa agatagctat gaatggatga tgggcacctg gctgagccgt 2280

attatcaccc agttcaacaa catcagctac cagatgtacg atagcctgaa ctatcaggcg 2340

ggtgcgatta aagcgaaaat cgatctggaa tacaaaaaat acagcggcag cgataaagaa 2400

aacatcaaaa gccaggttga aaacctgaaa aacagcctgg atgtgaaaat tagcgaagcg 2460

atgaataaca tcaacaaatt catccgcgaa tgcagcgtga cctacctgtt caaaaacatg 2520

ctgccgaaag tgatcgatga actgaacgaa tttgatcgca acaccaaagc gaaactgatc 2580

aacctgatcg atagccacaa cattattctg gtgggcgaag tggataaact gaaagcgaaa 2640

gttaacaaca gcttccagaa caccatcccg tttaacatct tcagctatac caacaacagc 2700

ctgctgaaag atatcatcaa cgaatacttc aatctagact ag 2742

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<211> 913
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 67

Gly Ser Glu Phe Met Pro Ile Thr Ile Asn Asn Phe Asn Tyr Ser Asp
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Pro Val Asp Asn Lys Asn Ile Leu Tyr Leu Asp Thr His Leu Asn Thr
20 25 30

Leu Ala Asn Glu Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn Ile Trp
35 40 45

Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys
50 55 60

Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr
65 70 75 80

Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys
85 90 95

Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr
100 105 110

Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile
115 120 125

Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr
130 135 140

Arg Gln Gly Asn Asn Trp Val Lys Thr Gly Ser Ile Asn Pro Ser Val
145 150 155 160

Ile Ile Thr Gly Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr Ser Thr
165 170 175

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Phe Lys Leu Thr Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe Gly Ala
            180                 185                 190

Leu Ser Ile Ile Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr Ser Asn
        195                 200                 205

Ala Thr Asn Asp Val Gly Glu Gly Arg Phe Ser Lys Ser Glu Phe Cys
    210                 215                 220

Met Asp Pro Ile Leu Ile Leu Met His Glu Leu Asn His Ala Met His
225                 230                 235                 240

Asn Leu Tyr Gly Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser Ser Val
                245                 250                 255

Thr Ser Asn Ile Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu Tyr Ala
            260                 265                 270

Glu Ile Tyr Ala Phe Gly Gly Pro Thr Ile Asp Leu Ile Pro Lys Ser
        275                 280                 285

Ala Arg Lys Tyr Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg Ser Ile
    290                 295                 300

Ala Lys Arg Leu Asn Ser Ile Thr Thr Ala Asn Pro Ser Ser Phe Asn
305                 310                 315                 320

Lys Tyr Ile Gly Glu Tyr Lys Gln Lys Leu Ile Arg Lys Tyr Arg Phe
                325                 330                 335

Val Val Glu Ser Ser Gly Glu Val Thr Val Asn Arg Asn Lys Phe Val
            340                 345                 350

Glu Leu Tyr Asn Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn Tyr Ala
        355                 360                 365

Lys Ile Tyr Asn Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn Val Tyr
    370                 375                 380

Thr Pro Val Thr Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp Ile Gln
385                 390                 395                 400

Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly
                405                 410                 415
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Gln Asn Leu Ser Arg Asn Pro Ala Leu Arg Lys Val Asn Pro Glu Asn
            420                 425                 430

Met Leu Tyr Leu Phe Thr Lys Phe Cys Val Asp Gly Ile Ile Thr Ser
        435                 440                 445

Lys Thr Lys Ser Leu Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala
    450                 455                 460

Arg Lys Ser Ala Arg Lys Arg Lys Asn Gln Ala Leu Ala Gly Gly Gly
465                 470                 475                 480

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu
                485                 490                 495

Gln Cys Arg Glu Leu Leu Val Lys Asn Thr Asp Leu Pro Phe Ile Gly
            500                 505                 510

Asp Ile Ser Asp Val Lys Thr Asp Ile Phe Leu Arg Lys Asp Ile Asn
        515                 520                 525

Glu Glu Thr Glu Val Ile Tyr Tyr Pro Asp Asn Val Ser Val Asp Gln
    530                 535                 540

Val Ile Leu Ser Lys Asn Thr Ser Glu His Gly Gln Leu Asp Leu Leu
545                 550                 555                 560

Tyr Pro Ser Ile Asp Ser Glu Ser Glu Ile Leu Pro Gly Glu Asn Gln
                565                 570                 575

Val Phe Tyr Asp Asn Arg Thr Gln Asn Val Asp Tyr Leu Asn Ser Tyr
            580                 585                 590

Tyr Tyr Leu Glu Ser Gln Lys Leu Ser Asp Asn Val Glu Asp Phe Thr
        595                 600                 605

Phe Thr Arg Ser Ile Glu Glu Ala Leu Asp Asn Ser Ala Lys Val Tyr
    610                 615                 620

Thr Tyr Phe Pro Thr Leu Ala Asn Lys Val Asn Ala Gly Val Gln Gly
625                 630                 635                 640

Gly Leu Phe Leu Met Trp Ala Asn Asp Val Val Glu Asp Phe Thr Thr
                645                 650                 655

Asn Ile Leu Arg Lys Asp Thr Leu Asp Lys Ile Ser Asp Val Ser Ala
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660 665 670

Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Ser Asn Ser Val Arg
675 680 685

Arg Gly Asn Phe Thr Glu Ala Phe Ala Val Thr Gly Val Thr Ile Leu
690 695 700

Leu Glu Ala Phe Pro Glu Phe Thr Ile Pro Ala Leu Gly Ala Phe Val
705 710 715 720

Ile Tyr Ser Lys Val Gln Glu Arg Asn Glu Ile Ile Lys Thr Ile Asp
725 730 735

Asn Cys Leu Glu Gln Arg Ile Lys Arg Trp Lys Asp Ser Tyr Glu Trp
740 745 750

Met Met Gly Thr Trp Leu Ser Arg Ile Ile Thr Gln Phe Asn Asn Ile
755 760 765

Ser Tyr Gln Met Tyr Asp Ser Leu Asn Tyr Gln Ala Gly Ala Ile Lys
770 775 780

Ala Lys Ile Asp Leu Glu Tyr Lys Lys Tyr Ser Gly Ser Asp Lys Glu
785 790 795 800

Asn Ile Lys Ser Gln Val Glu Asn Leu Lys Asn Ser Leu Asp Val Lys
805 810 815

Ile Ser Glu Ala Met Asn Asn Ile Asn Lys Phe Ile Arg Glu Cys Ser
820 825 830

Val Thr Tyr Leu Phe Lys Asn Met Leu Pro Lys Val Ile Asp Glu Leu
835 840 845

Asn Glu Phe Asp Arg Asn Thr Lys Ala Lys Leu Ile Asn Leu Ile Asp
850 855 860

Ser His Asn Ile Ile Leu Val Gly Glu Val Asp Lys Leu Lys Ala Lys
865 870 875 880

Val Asn Asn Ser Phe Gln Asn Thr Ile Pro Phe Asn Ile Phe Ser Tyr
885 890 895

Thr Asn Asn Ser Leu Leu Lys Asp Ile Ile Asn Glu Tyr Phe Asn Leu
900 905 910

Asp

<210> 68
<211> 2673
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 68
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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

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tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

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actaaatctc tgatagaagg tagatacggt ggtttcctgg cgctagcggg cggtggcggt 1380

agcggcggtg gcggtagcgg cggtggcggt agcgcactag tgctgcagtg tatcaaggtt 1440

aacaactggg atttattctt cagcccgagt gaagacaact tcaccaacga cctgaacaaa 1500

ggtgaagaaa tcacctcaga tactaacatc gaagcagccg aagaaaacat ctcgctggac 1560

ctgatccagc agtactacct gacctttaat ttcgacaacg agccggaaaa catttctatc 1620

gaaaacctga gctctgatat catcggccag ctggaactga tgccgaacat cgaacgtttc 1680

ccaaacggta aaaagtacga gctggacaaa tataccatgt tccactacct gcgcgcgcag 1740

gaatttgaac acggcaaatc ccgtatcgca ctgactaact ccgttaacga agctctgctc 1800

aacccgtccc gtgtatacac cttcttctct agcgactacg tgaaaaaggt caacaaagcg 1860

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gcgctgagca aacgtaacga aaaatgggat gaagtttaca aatatatcgt gaccaactgg 2220

ctggctaagg ttaatactca gatcgacctc atccgcaaaa aaatgaaaga agcactggaa 2280

aaccaggcgg aagctaccaa ggcaatcatt aactaccagt acaaccagta caccgaggaa 2340

gaaaaaaaca acatcaactt caacatcgac gatctgtcct ctaaactgaa cgaatccatc 2400

aacaaagcta tgatcaacat caacaagttc ctgaaccagt gctctgtaag ctatctgatg 2460

aactccatga tcccgtacgg tgttaaacgt ctggaggact tcgatgcgtc tctgaaagac 2520

gccctgctga aatacattta cgacaaccgt ggcactctga tcggtcaggt tgatcgtctg 2580

aaggacaaag tgaacaatac cttatcgacc gacatccctt ttcagctcag taaatatgtc 2640

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<211> 890
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 69

Gly Ser Met Glu Phe Val Asn Lys Gln Phe Asn Tyr Lys Asp Pro Val
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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
        35                  40                  45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
    50                  55                  60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65                  70                  75                  80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
                85                  90                  95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
            100                 105                 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270
```

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Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Tyr Gly Gly Phe Leu Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly
    450                 455                 460

Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val
465                 470                 475                 480

Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn
                485                 490                 495

Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala
            500                 505                 510
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Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr
515 520 525

Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser
530 535 540

Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe
545 550 555 560

Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr
565 570 575

Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr
580 585 590

Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe
595 600 605

Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala
610 615 620

Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu
625 630 635 640

Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile
645 650 655

Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys
660 665 670

Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu
675 680 685

Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu
690 695 700

Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn
705 710 715 720

Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile
725 730 735

Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg
740 745 750

Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala

755 760 765

Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn
770 775 780

Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile
785 790 795 800

Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val
805 810 815

Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu
820 825 830

Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp
835 840 845

Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val
850 855 860

Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val
865 870 875 880

Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
885 890

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<213> Artificial Sequence

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<223> Synthetic

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attgcttaca tcaaaatccc gaacgctggc cagatgcagc cggtaaaggc attcaaaatc 120

cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

ttcactggtc tgttcgagtt ttacaagctg ctgtgcgtcg acggcatcat tacctccaaa 1320

actaaatctc tgatagaagg tagatatggc ggtttcacgg gcgcacgcaa atcagcgcgt 1380

aaattagcta accaggcgct agcgggcggt ggcggtagcg gcggtggcgg tagcggcggt 1440

ggcggtagcg cactagtgct gcagtgtatc aaggttaaca actgggattt attcttcagc 1500

ccgagtgaag acaacttcac caacgacctg aacaaaggtg aagaaatcac ctcagatact 1560

aacatcgaag cagccgaaga aaacatctcg ctggacctga tccagcagta ctacctgacc 1620

tttaatttcg acaacgagcc ggaaaacatt tctatcgaaa acctgagctc tgatatcatc 1680

ggccagctgg aactgatgcc gaacatcgaa cgtttcccaa acggtaaaaa gtacgagctg 1740

gacaaatata ccatgttcca ctacctgcgc gcgcaggaat ttgaacacgg caaatcccgt 1800

atcgcactga ctaactccgt taacgaagct ctgctcaacc cgtcccgtgt atacaccttc 1860

ttctctagcg actacgtgaa aaaggtcaac aaagcgactg aagctgcaat gttcttgggt 1920

tgggttgaac agcttgttta tgattttacc gacgagacgt ccgaagtatc tactaccgac 1980

aaaattgcgg atatcactat catcatcccg tacatcggtc cggctctgaa cattggcaac 2040

atgctgtaca aagacgactt cgttggcgca ctgatcttct ccggtgcggt gatcctgctg 2100

gagttcatcc cggaaatcgc catcccggta ctgggcacct ttgctctggt ttcttacatt 2160

gcaaacaagg ttctgactgt acaaaccatc gacaacgcgc tgagcaaacg taacgaaaaa 2220

tgggatgaag tttacaaata tatcgtgacc aactggctgg ctaaggttaa tactcagatc 2280

gacctcatcc gcaaaaaaat gaaagaagca ctggaaaacc aggcggaagc taccaaggca 2340

atcattaact accagtacaa ccagtacacc gaggaagaaa aaaacaacat caacttcaac 2400

atcgacgatc tgtcctctaa actgaacgaa tccatcaaca aagctatgat caacatcaac 2460

aagttcctga accagtgctc tgtaagctat ctgatgaact ccatgatccc gtacggtgtt 2520

aaacgtctgg aggacttcga tgcgtctctg aaagacgccc tgctgaaata catttacgac 2580

aaccgtggca ctctgatcgg tcaggttgat cgtctgaagg acaaagtgaa caatacctta 2640

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ctagactag 2709

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<223> Synthetic

<400> 71

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
85 90 95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
100 105 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
115 120 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
130 135 140

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Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
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385 390 395 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
405 410 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
420 425 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
435 440 445

Tyr Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Leu Ala Asn
450 455 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465 470 475 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
485 490 495

Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
500 505 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
515 520 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
530 535 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
545 550 555 560

Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
565 570 575

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
580 585 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
595 600 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
610 615 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
625 630 635 640

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Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
                645                 650                 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
            660                 665                 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val
        675                 680                 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
    690                 695                 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705                 710                 715                 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
                725                 730                 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
            740                 745                 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
        755                 760                 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
    770                 775                 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785                 790                 795                 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
                805                 810                 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
            820                 825                 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
        835                 840                 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
    850                 855                 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865                 870                 875                 880
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Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Asp
900

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<211> 2709
<212> DNA
<213> Artificial Sequence

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<223> Synthetic

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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

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actaaatctc tgatagaagg tagatatggc ggtttcacgg gcgcacgcaa atcagcgcgt 1380

aaacgtaaga accaggcgct agcgggcggt ggcggtagcg gcggtggcgg tagcggcggt 1440

ggcggtagcg cactagtgct gcagtgtatc aaggttaaca actgggattt attcttcagc 1500

ccgagtgaag acaacttcac caacgacctg aacaaaggtg aagaaatcac ctcagatact 1560

aacatcgaag cagccgaaga aaacatctcg ctggacctga tccagcagta ctacctgacc 1620

tttaatttcg acaacgagcc ggaaaacatt tctatcgaaa acctgagctc tgatatcatc 1680

ggccagctgg aactgatgcc gaacatcgaa cgtttcccaa acggtaaaaa gtacgagctg 1740

gacaaatata ccatgttcca ctacctgcgc gcgcaggaat ttgaacacgg caaatcccgt 1800

atcgcactga ctaactccgt taacgaagct ctgctcaacc cgtcccgtgt atacaccttc 1860

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tgggttgaac agcttgttta tgattttacc gacgagacgt ccgaagtatc tactaccgac 1980

aaaattgcgg atatcactat catcatcccg tacatcggtc cggctctgaa cattggcaac 2040

atgctgtaca aagacgactt cgttggcgca ctgatcttct ccggtgcggt gatcctgctg 2100

gagttcatcc cggaaatcgc catcccggta ctgggcacct ttgctctggt ttcttacatt 2160

gcaaacaagg ttctgactgt acaaaccatc gacaacgcgc tgagcaaacg taacgaaaaa 2220

tgggatgaag tttacaaata tatcgtgacc aactggctgg ctaaggttaa tactcagatc 2280

gacctcatcc gcaaaaaaat gaaagaagca ctggaaaacc aggcggaagc taccaaggca 2340

atcattaact accagtacaa ccagtacacc gaggaagaaa aaaacaacat caacttcaac 2400

atcgacgatc tgtcctctaa actgaacgaa tccatcaaca aagctatgat caacatcaac 2460

aagttcctga accagtgctc tgtaagctat ctgatgaact ccatgatccc gtacggtgtt 2520

aaacgtctgg aggacttcga tgcgtctctg aaagacgccc tgctgaaata catttacgac 2580

aaccgtggca ctctgatcgg tcaggttgat cgtctgaagg acaaagtgaa caatacctta 2640

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ctagactag 2709

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<212> PRT
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<400> 73

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
            20                  25                  30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
        35                  40                  45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
    50                  55                  60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65                  70                  75                  80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
                85                  90                  95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
            100                 105                 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255
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Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Tyr Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
                485                 490                 495
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Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
            500                 505                 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
        515                 520                 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
    530                 535                 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
545                 550                 555                 560

Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
                565                 570                 575

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
            580                 585                 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
        595                 600                 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
    610                 615                 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
625                 630                 635                 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
                645                 650                 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
            660                 665                 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val
        675                 680                 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
    690                 695                 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705                 710                 715                 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
                725                 730                 735
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Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
740 745 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
755 760 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
770 775 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785 790 795 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Asp
900

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<212> DNA
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35 40 45

Met Ile Asp Phe Ser Val Ala Asp Val Asn Lys Arg Ile Ala Thr Val
50 55 60

Val Asp Pro Gln Tyr Ala Val Ser Val Lys His Ala Lys Ala Glu Val
65 70 75 80

His Thr Phe Tyr Tyr Gly Gln Tyr Asn Gly His Asn Asp Val Ala Asp
85 90 95

Lys Glu Asn Glu Tyr Arg Val Val Glu Gln Asn Asn Tyr Glu Pro His
100 105 110

Lys Ala Trp Gly Ala Ser Asn Leu Gly Arg Leu Glu Asp Tyr Asn Met
115 120 125

Ala Arg Phe Asn Lys Phe Val Thr Glu Val Ala Pro Ile Ala Pro Thr
130 135 140

Asp Ala Gly Gly Gly Leu Asp Thr Tyr Lys Asp Lys Asn Arg Phe Ser
145 150 155 160

Ser Phe Val Arg Ile Gly Ala Gly Arg Gln Leu Val Tyr Glu Lys Gly
165 170 175

Val Tyr His Gln Glu Gly Asn Glu Lys Gly Tyr Asp Leu Arg Asp Leu
180 185 190

Ser Gln Ala Tyr Arg Tyr Ala Ile Ala Gly Thr Pro Tyr Lys Asp Ile
195 200 205

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Asn Ile Asp Gln Thr Met Asn Thr Glu Gly Leu Ile Gly Phe Gly Asn
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His Asn Lys Gln Tyr Ser Ala Glu Glu Leu Lys Gln Ala Leu Ser Gln
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Asp Ala Leu Thr Asn Tyr Gly Val Leu Gly Asp Ser Gly Ser Pro Leu
                245                 250                 255

Phe Ala Phe Asp Lys Gln Lys Asn Gln Trp Val Phe Leu Gly Thr Tyr
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Asp Tyr Trp Ala Gly Tyr Gly Lys Lys Ser Trp Gln Glu Trp Asn Ile
        275                 280                 285

Tyr Lys Lys Glu Phe Ala Asp Lys Ile Lys Gln His Asp Asn Ala Gly
    290                 295                 300

Thr Val Lys Gly Asn Gly Glu His His Trp Lys Thr Thr Gly Thr Asn
305                 310                 315                 320

Ser His Ile Gly Ser Thr Ala Val Arg Leu Ala Asn Asn Glu Gly Asp
                325                 330                 335

Ala Asn Asn Gly Gln Asn Val Thr Phe Glu Asp Asn Gly Thr Leu Val
            340                 345                 350

Leu Asn Gln Asn Ile Asn Gln Gly Ala Gly Gly Leu Phe Phe Lys Gly
        355                 360                 365

Asp Tyr Thr Val Lys Gly Ala Asn Asn Asp Ile Thr Trp Leu Gly Ala
    370                 375                 380

Gly Ile Asp Val Ala Asp Gly Lys Lys Val Val Trp Gln Val Lys Asn
385                 390                 395                 400

Pro Asn Gly Asp Arg Leu Ala Lys Ile Gly Lys Gly Thr Leu Glu Ile
                405                 410                 415

Asn Gly Thr Gly Val Asn Gln Gly Gln Leu Lys Val Gly Asp Gly Thr
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Val Ile Leu Asn Gln Lys Ala Asp Ala Asp Lys Lys Val Gln Ala Phe
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Ser Gln Val Gly Ile Val Ser Gly Arg Gly Thr Leu Val Leu Asn Ser
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Ser Asn Gln Ile Asn Pro Asp Asn Leu Tyr Phe Gly Phe Arg Gly Gly
465                 470                 475                 480

Arg Leu Asp Ala Asn Gly Asn Asp Leu Thr Phe Glu His Ile Arg Asn
                485                 490                 495

Val Asp Glu Gly Ala Arg Ile Val Asn His Asn Thr Asp His Ala Ser
            500                 505                 510

Thr Ile Thr Leu Thr Gly Lys Ser Leu Ile Thr Asn Pro Asn Ser Leu
        515                 520                 525

Ser Val His Ser Ile Gln Asn Asp Tyr Asp Glu Asp Asp Tyr Ser Tyr
    530                 535                 540

Tyr Tyr Arg Pro Arg Arg Pro Ile Pro Gln Gly Lys Asp Leu Tyr Tyr
545                 550                 555                 560

Lys Asn Tyr Arg Tyr Tyr Ala Leu Lys Ser Gly Gly Arg Leu Asn Ala
                565                 570                 575

Pro Met Pro Glu Asn Gly Val Ala Glu Asn Asn Asp Trp Ile Phe Met
            580                 585                 590

Gly Tyr Thr Gln Glu Glu Ala Arg Lys Asn Ala Met Asn His Lys Asn
        595                 600                 605

Asn Arg Arg Ile Gly Asp Phe Gly Gly Phe Phe Asp Glu Glu Asn Gly
    610                 615                 620

Lys Gly His Asn Gly Ala Leu Asn Leu Asn Phe Asn Gly Lys Ser Ala
625                 630                 635                 640

Gln Lys Arg Phe Leu Leu Thr Gly Gly Ala Asn Leu Asn Gly Lys Ile
                645                 650                 655

Ser Val Thr Gln Gly Asn Val Leu Leu Ser Gly Arg Pro Thr Pro His
            660                 665                 670

Ala Arg Asp Phe Val Asn Lys Ser Ser Ala Arg Lys Asp Ala His Phe
        675                 680                 685
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Ser Lys Asn Asn Glu Val Val Phe Glu Asp Asp Trp Ile Asn Arg Thr
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Phe Lys Ala Ala Glu Ile Ala Val Asn Gln Ser Ala Ser Phe Ser Ser
705                 710                 715                 720

Gly Arg Asn Val Ser Asp Ile Thr Ala Asn Ile Thr Ala Thr Asp Asn
                725                 730                 735

Ala Lys Val Asn Leu Gly Tyr Lys Asn Gly Asp Glu Val Cys Val Arg
            740                 745                 750

Ser Asp Tyr Thr Gly Tyr Val Thr Cys Asn Thr Gly Asn Leu Ser Asp
        755                 760                 765

Lys Ala Leu Asn Ser Phe Asp Ala Thr Arg Ile Asn Gly Asn Val Asn
    770                 775                 780

Leu Asn Gln Asn Ala Ala Leu Val Leu Gly Lys Ala Ala Leu Trp Gly
785                 790                 795                 800

Lys Ile Gln Gly Gln Gly Asn Ser Arg Val Ser Leu Asn Gln His Ser
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Lys Trp His Leu Thr Gly Asp Ser Gln Val His Asn Leu Ser Leu Ala
            820                 825                 830

Asp Ser His Ile His Leu Asn Asn Ala Ser Asp Ala Gln Ser Ala Asn
        835                 840                 845

Lys Tyr His Thr Ile Lys Ile Asn His Leu Ser Gly Asn Gly His Phe
    850                 855                 860

His Tyr Leu Thr Asp Leu Ala Lys Asn Leu Gly Asp Lys Val Leu Val
865                 870                 875                 880

Lys Glu Ser Ala Ser Gly His Tyr Gln Leu His Val Gln Asn Lys Thr
                885                 890                 895

Gly Glu Pro Asn Gln Glu Gly Leu Asp Leu Phe Asp Ala Ser Ser Val
            900                 905                 910

Gln Asp Arg Ser Arg Leu Phe Val Ser Leu Ala Asn His Tyr Val Asp
        915                 920                 925

Leu Gly Ala Leu Arg Tyr Thr Ile Lys Thr Glu Asn Gly Ile Thr Arg
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Leu Tyr Asn Pro Tyr Ala Gly Asn Gly Arg Pro Val Lys Pro Ala Pro
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Cys Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly
                965                 970                 975

Arg Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys
            980                 985                 990

Asn Gln Ala Leu Ala Gly Gly Gly  Gly Ser Gly Gly Gly  Gly Ser Gly
        995                 1000                1005

Gly Gly  Gly Ser Ala Leu Val  Leu Gln Cys Ile Lys  Val Asn Asn
    1010                1015                1020

Trp Asp  Leu Phe Phe Ser Pro  Ser Glu Asp Asn Phe  Thr Asn Asp
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Leu Asn  Lys Gly Glu Glu Ile  Thr Ser Asp Thr Asn  Ile Glu Ala
    1040                1045                1050

Ala Glu  Glu Asn Ile Ser Leu  Asp Leu Ile Gln Gln  Tyr Tyr Leu
    1055                1060                1065

Thr Phe  Asn Phe Asp Asn Glu  Pro Glu Asn Ile Ser  Ile Glu Asn
    1070                1075                1080

Leu Ser  Ser Asp Ile Ile Gly  Gln Leu Glu Leu Met  Pro Asn Ile
    1085                1090                1095

Glu Arg  Phe Pro Asn Gly Lys  Lys Tyr Glu Leu Asp  Lys Tyr Thr
    1100                1105                1110

Met Phe  His Tyr Leu Arg Ala  Gln Glu Phe Glu His  Gly Lys Ser
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Arg Ile  Ala Leu Thr Asn Ser  Val Asn Glu Ala Leu  Leu Asn Pro
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Ser Arg  Val Tyr Thr Phe Phe  Ser Ser Asp Tyr Val  Lys Lys Val
    1145                1150                1155

Asn Lys  Ala Thr Glu Ala Ala  Met Phe Leu Gly Trp  Val Glu Gln
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Asp Lys  Ile Ala Asp Ile Thr  Ile Ile Ile Pro Tyr  Ile Gly Pro
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Ala Leu  Asn Ile Gly Asn Met  Leu Tyr Lys Asp Asp  Phe Val Gly
     1205                 1210                 1215

Ala Leu  Ile Phe Ser Gly Ala  Val Ile Leu Leu Glu  Phe Ile Pro
     1220                 1225                 1230

Glu Ile  Ala Ile Pro Val Leu  Gly Thr Phe Ala Leu  Val Ser Tyr
     1235                 1240                 1245

Ile Ala  Asn Lys Val Leu Thr  Val Gln Thr Ile Asp  Asn Ala Leu
     1250                 1255                 1260

Ser Lys  Arg Asn Glu Lys Trp  Asp Glu Val Tyr Lys  Tyr Ile Val
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Thr Asn  Trp Leu Ala Lys Val  Asn Thr Gln Ile Asp  Leu Ile Arg
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Lys Lys  Met Lys Glu Ala Leu  Glu Asn Gln Ala Glu  Ala Thr Lys
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Ala Ile  Ile Asn Tyr Gln Tyr  Asn Gln Tyr Thr Glu  Glu Glu Lys
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Asn Asn  Ile Asn Phe Asn Ile  Asp Asp Leu Ser Ser  Lys Leu Asn
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Glu Ser  Ile Asn Lys Ala Met  Ile Asn Ile Asn Lys  Phe Leu Asn
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Gln Cys  Ser Val Ser Tyr Leu  Met Asn Ser Met Ile  Pro Tyr Gly
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Val Lys  Arg Leu Glu Asp Phe  Asp Ala Ser Leu Lys  Asp Ala Leu
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Leu Lys  Tyr Ile Tyr Asp Asn  Arg Gly Thr Leu Ile  Gly Gln Val
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cggtcaggtt gatcgtctga aggacaaagt gaacaatacc ttatcgaccg acatcccttt 1260

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aagtgggcac catcaccatc accattaatg aaagctt 1357

<210> 78
<211> 2745
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 78
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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

gataaacttt acaaaatgct gactgaaatt tacaccgaag acaacttcgt taagttcttt 1080

aaagttctga accgcaaaac ctatctgaac ttcgacaagg cagtattcaa aatcaacatc 1140

gtgccgaaag ttaactacac tatctacgat ggtttcaacc tgcgtaacac caacctggct 1200

gctaatttta acggccagaa cacggaaatc aacaacatga acttcacaaa actgaaaaac 1260

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actaaatctc tgatagaagg tagatttggc ggtttcacgg gcgcacgcaa atcagcgcgt 1380

aaacgtaaga accaggcgct agcgggcggt ggcggtagcg gcggtggcgg tagcggcggt 1440

ggcggtagcg cactagtgct gcagtgtatc aaggttaaca actgggattt attcttcagc 1500

ccgagtgaag acaacttcac caacgacctg aacaaaggtg aagaaatcac ctcagatact 1560

aacatcgaag cagccgaaga aaacatctcg ctggacctga tccagcagta ctacctgacc 1620

tttaatttcg acaacgagcc ggaaaacatt tctatcgaaa acctgagctc tgatatcatc 1680

ggccagctgg aactgatgcc gaacatcgaa cgtttcccaa acggtaaaaa gtacgagctg 1740

gacaaatata ccatgttcca ctacctgcgc gcgcaggaat ttgaacacgg caaatcccgt 1800

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<211> 914
<212> PRT
<213> Artificial Sequence

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<223> Synthetic

<400> 79

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Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
        35                  40                  45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
    50                  55                  60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65                  70                  75                  80

Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
                85                  90                  95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
            100                 105                 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255
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Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320

Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Lys Val Asn Asn Trp Asp
                485                 490                 495
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Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn Lys
            500                 505                 510

Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn
        515                 520                 525

Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe Asp
    530                 535                 540

Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile
545                 550                 555                 560

Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly Lys
                565                 570                 575

Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala Gln
            580                 585                 590

Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn
        595                 600                 605

Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp
    610                 615                 620

Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly
625                 630                 635                 640

Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val
                645                 650                 655

Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr Ile
            660                 665                 670

Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val
        675                 680                 685

Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile Pro
    690                 695                 700

Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile
705                 710                 715                 720

Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys
                725                 730                 735

Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn Trp
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740 745 750

Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met Lys
755 760 765

Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr
770 775 780

Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn
785 790 795 800

Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala Met
805 810 815

Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met
820 825 830

Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala
835 840 845

Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr
850 855 860

Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu
865 870 875 880

Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg
885 890 895

Leu Leu Ser Thr Leu Glu Ile Glu Gly Arg Ser Gly His His His His
900 905 910

His His

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<211> 619
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 80
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gctgcagtgt atcaatctgg attgggacgt aatccgtgat aagaccaaaa caaaaatcga 120

gtcttgtgaaa gaacacggcc cgatcaaaaa taagatgtct gaatcaccca ataaaactgt 180

ttcggaggaa aaagcgaaac agtatttgga agagtttcat caaaccgcgc ttgaacatcc 240

ggagctcagt gaactgaaaa cagtgacggg aacgaatcct gtttttgcag gcgcaaacta 300

tgcggcttgg gccgtgaatg ttgcccaagt aattgatagt gagaccgcag acaacctgga 360

aaagacgacc gcagcgttaa gcattttacc ggggattggt tccgtgatgg gtatagcgga 420

tggagcggtc caccataaca ctgaggaaat tgtcgcccag tcaatcgctc tgagttccct 480

gatggttgca caggctatcc cactcgtggg ggaactggtt gacataggtt tcgccgccta 540

caacttcgta gaaagcatta ttaatctttt tcaggtggtg cataacagct acaaccgccc 600

tctagaatga taaaagctt 619

<210> 81
<211> 1971
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 81
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cacaacaaaa tctgggttat cccggaacgt gataccttta ctaacccgga agaaggtgac 180

ctgaacccgc caccggaagc gaaacaggtg ccggtatctt actatgactc cacctacctg 240

tctaccgata acgaaaagga caactacctg aaaggtgtta ctaaactgtt cgagcgtatt 300

tactccaccg acctgggccg tatgctgctg actagcatcg ttcgcggtat cccgttctgg 360

ggcggttcta ccatcgatac cgaactgaaa gtaatcgaca ctaactgcat caacgttatt 420

cagccggacg gttcctatcg ttccgaagaa ctgaacctgg tgatcatcgg cccgtctgct 480

gatatcatcc agttcgagtg taagagcttt ggtcacgaag ttctgaacct cacccgtaac 540

ggctacggtt ccactcagta catccgtttc tctccggact tcaccttcgg ttttgaagaa 600

tccctggaag tagacacgaa cccactgctg ggcgctggta aattcgcaac tgatcctgcg 660

gttaccctgg ctcacgaact gattcatgca ggccaccgcc tgtacggtat cgccatcaat 720

ccgaaccgtg tcttcaaagt taacaccaac gcgtattacg agatgtccgg tctggaagtt 780

agcttcgaag aactgcgtac ttttggcggt cacgacgcta aattcatcga ctctctgcaa 840

gaaaacgagt tccgtctgta ctactataac aagttcaaag atatcgcatc caccctgaac 900

aaagcgaaat ccatcgtggg taccactgct tctctccagt acatgaagaa cgtttttaaa 960

gaaaaatacc tgctcagcga agacacctcc ggcaaattct ctgtagacaa gttgaaattc 1020

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gattgggacg taatccgtga taagaccaaa acaaaaatcg agtctttgaa agaacacggc 1500

ccgatcaaaa ataagatgtc tgaatcaccc aataaaactg tttcggagga aaaagcgaaa 1560

cagtatttgg aagagtttca tcaaaccgcg cttgaacatc cggagctcag tgaactgaaa 1620

acagtgacgg gaacgaatcc tgtttttgca ggcgcaaact atgcggcttg ggccgtgaat 1680

gttgcccaag taattgatag tgagaccgca gacaacctgg aaaagacgac cgcagcgtta 1740

agcattttac cggggattgg ttccgtgatg ggtatagcgg atggagcggt ccaccataac 1800

actgaggaaa ttgtcgccca gtcaatcgct ctgagttccc tgatggttgc acaggctatc 1860

ccactcgtgg gggaactggt tgacataggt ttcgccgcct acaacttcgt agaaagcatt 1920

attaatcttt ttcaggtggt gcataacagc tacaaccgcc ctctagaatg a 1971

<210> 82
<211> 656
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 82

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Asn Gly Val Asp Ile Ala Tyr Ile Lys Ile Pro Asn Ala Gly Gln Met
20 25 30

Gln Pro Val Lys Ala Phe Lys Ile His Asn Lys Ile Trp Val Ile Pro
35 40 45

Glu Arg Asp Thr Phe Thr Asn Pro Glu Glu Gly Asp Leu Asn Pro Pro
50 55 60

Pro Glu Ala Lys Gln Val Pro Val Ser Tyr Tyr Asp Ser Thr Tyr Leu
65 70 75 80

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Ser Thr Asp Asn Glu Lys Asp Asn Tyr Leu Lys Gly Val Thr Lys Leu
                85                  90                  95

Phe Glu Arg Ile Tyr Ser Thr Asp Leu Gly Arg Met Leu Leu Thr Ser
            100                 105                 110

Ile Val Arg Gly Ile Pro Phe Trp Gly Gly Ser Thr Ile Asp Thr Glu
        115                 120                 125

Leu Lys Val Ile Asp Thr Asn Cys Ile Asn Val Ile Gln Pro Asp Gly
    130                 135                 140

Ser Tyr Arg Ser Glu Glu Leu Asn Leu Val Ile Ile Gly Pro Ser Ala
145                 150                 155                 160

Asp Ile Ile Gln Phe Glu Cys Lys Ser Phe Gly His Glu Val Leu Asn
                165                 170                 175

Leu Thr Arg Asn Gly Tyr Gly Ser Thr Gln Tyr Ile Arg Phe Ser Pro
            180                 185                 190

Asp Phe Thr Phe Gly Phe Glu Glu Ser Leu Glu Val Asp Thr Asn Pro
        195                 200                 205

Leu Leu Gly Ala Gly Lys Phe Ala Thr Asp Pro Ala Val Thr Leu Ala
    210                 215                 220

His Glu Leu Ile His Ala Gly His Arg Leu Tyr Gly Ile Ala Ile Asn
225                 230                 235                 240

Pro Asn Arg Val Phe Lys Val Asn Thr Asn Ala Tyr Tyr Glu Met Ser
                245                 250                 255

Gly Leu Glu Val Ser Phe Glu Glu Leu Arg Thr Phe Gly Gly His Asp
            260                 265                 270

Ala Lys Phe Ile Asp Ser Leu Gln Glu Asn Glu Phe Arg Leu Tyr Tyr
        275                 280                 285

Tyr Asn Lys Phe Lys Asp Ile Ala Ser Thr Leu Asn Lys Ala Lys Ser
    290                 295                 300

Ile Val Gly Thr Thr Ala Ser Leu Gln Tyr Met Lys Asn Val Phe Lys
305                 310                 315                 320
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Glu Lys Tyr Leu Leu Ser Glu Asp Thr Ser Gly Lys Phe Ser Val Asp
                325                 330                 335

Lys Leu Lys Phe Asp Lys Leu Tyr Lys Met Leu Thr Glu Ile Tyr Thr
            340                 345                 350

Glu Asp Asn Phe Val Lys Phe Phe Lys Val Leu Asn Arg Lys Thr Tyr
        355                 360                 365

Leu Asn Phe Asp Lys Ala Val Phe Lys Ile Asn Ile Val Pro Lys Val
    370                 375                 380

Asn Tyr Thr Ile Tyr Asp Gly Phe Asn Leu Arg Asn Thr Asn Leu Ala
385                 390                 395                 400

Ala Asn Phe Asn Gly Gln Asn Thr Glu Ile Asn Asn Met Asn Phe Thr
                405                 410                 415

Lys Leu Lys Asn Phe Thr Gly Leu Phe Glu Phe Tyr Lys Leu Leu Cys
            420                 425                 430

Val Asp Gly Ile Ile Thr Ser Lys Thr Lys Ser Leu Ile Glu Gly Arg
        435                 440                 445

Tyr Gly Gly Phe Leu Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly
    450                 455                 460

Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu Gln Cys Ile Asn Leu
465                 470                 475                 480

Asp Trp Asp Val Ile Arg Asp Lys Thr Lys Thr Lys Ile Glu Ser Leu
                485                 490                 495

Lys Glu His Gly Pro Ile Lys Asn Lys Met Ser Glu Ser Pro Asn Lys
            500                 505                 510

Thr Val Ser Glu Glu Lys Ala Lys Gln Tyr Leu Glu Glu Phe His Gln
        515                 520                 525

Thr Ala Leu Glu His Pro Glu Leu Ser Glu Leu Lys Thr Val Thr Gly
    530                 535                 540

Thr Asn Pro Val Phe Ala Gly Ala Asn Tyr Ala Ala Trp Ala Val Asn
545                 550                 555                 560
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Val Ala Gln Val Ile Asp Ser Glu Thr Ala Asp Asn Leu Glu Lys Thr
565 570 575

Thr Ala Ala Leu Ser Ile Leu Pro Gly Ile Gly Ser Val Met Gly Ile
580 585 590

Ala Asp Gly Ala Val His His Asn Thr Glu Glu Ile Val Ala Gln Ser
595 600 605

Ile Ala Leu Ser Ser Leu Met Val Ala Gln Ala Ile Pro Leu Val Gly
610 615 620

Glu Leu Val Asp Ile Gly Phe Ala Ala Tyr Asn Phe Val Glu Ser Ile
625 630 635 640

Ile Asn Leu Phe Gln Val Val His Asn Ser Tyr Asn Arg Pro Leu Glu
645 650 655

<210> 83
<211> 1329
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 83
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cgtacggaca gcgataaaga ccgcttctta cagaccatgg tcaaactttt taaccgtatt 300

aagaacaatg tggccggaga agcactcttg gataagatta tcaacgcgat tccatacctg 360

ggcaattctt acagcctgct ggataaattt gacacaaata gtaattcagt cagctttaac 420

ctgttagaac aagatccgag tggcgcaacc acgaagtctg ccatgctgac aaatctgatc 480

atttttggtc caggtcctgt actgaataaa aatgaagtac gcggcatcgt tctccgcgtg 540

gacaataaga actacttccc atgccgtgac ggcttcggtt cgatcatgca gatggctttc 600

tgtccggagt acgttccgac gtttgataat gttattgaga atatcacgag tttaacaatc 660

ggtaagtcaa aatattttca agatccggcc cttctcctta tgcatgaact gattcacgtg 720

ctgcacggct tatatggtat gcaagtgtcc tcgcatgaaa tcattccgtc caaacaggaa 780

atttatatgc agcataccta cccgatttca gctgaagagt tgtttacgtt tggtggccag 840

gacgcgaatt tgatctccat cgacatcaaa aacgatctgt atgagaaaac attaaatgac 900

tataaagcga ttgcgaacaa actgtctcag gtgactagct gcaacgatcc taacattgat 960

attgattcct acaaacaaat ttatcaacag aaataccagt tcgataaaga cagcaatggt 1020

cagtatatcg taaacgaaga taaatttcag atcctgtata acagcattat gtatggcttt 1080

accgaaattg agttggggaa gaaatttaac attaaaaccc gtctgtctta ttttagtatg 1140

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gggttcaaca ttgaatctaa ggatctgaaa tccgaataca aaggccaaaa tatgcgtgtt 1260

aatactaacg ctttccgtaa tgttgatggt agtggactcg tctcgaaact gattgggttg 1320

tgtgtcgac 1329

<210> 84
<211> 2736
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 84
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tttaacccgc cttcatcgct gatcgaagga gcatcagagt attacgatcc gaactatctg 240

cgtacggaca gcgataaaga ccgcttctta cagaccatgg tcaaactttt taaccgtatt 300

aagaacaatg tggccggaga agcactcttg gataagatta tcaacgcgat tccatacctg 360

ggcaattctt acagcctgct ggataaattt gacacaaata gtaattcagt cagctttaac 420

ctgttagaac aagatccgag tggcgcaacc acgaagtctg ccatgctgac aaatctgatc 480

atttttggtc caggtcctgt actgaataaa aatgaagtac gcggcatcgt tctccgcgtg 540

gacaataaga actacttccc atgccgtgac ggcttcggtt cgatcatgca gatggctttc 600

tgtccggagt acgttccgac gtttgataat gttattgaga atatcacgag tttaacaatc 660

ggtaagtcaa aatattttca agatccggcc cttctcctta tgcatgaact gattcacgtg 720

ctgcacggct tatatggtat gcaagtgtcc tcgcatgaaa tcattccgtc caaacaggaa 780

atttatatgc agcataccta cccgatttca gctgaagagt tgtttacgtt tggtggccag 840

gacgcgaatt tgatctccat cgacatcaaa aacgatctgt atgagaaaac attaaatgac 900

tataaagcga ttgcgaacaa actgtctcag gtgactagct gcaacgatcc taacattgat 960

attgattcct acaaacaaat ttatcaacag aaataccagt tcgataaaga cagcaatggt 1020

cagtatatcg taaacgaaga taaatttcag atcctgtata acagcattat gtatggcttt 1080

accgaaattg agttggggaa gaaatttaac attaaaaccc gtctgtctta ttttagtatg 1140

aaccatgatc cggtgaaaat ccccaatctg cttgatgata ccatttataa tgataccgaa 1200

gggttcaaca ttgaatctaa ggatctgaaa tccgaataca aaggccaaaa tatgcgtgtt 1260

aatactaacg ctttccgtaa tgttgatggt agtggactcg tctcgaaact gattgggttg 1320

tgtgtcgacg gcatcattac ctccaaaact aaatctctga tagaaggtag atttggcggt 1380

ttcacgggcg cacgcaaatc agcgcgtaaa cgtaagaacc aggcgctagc gggcggtggc 1440

ggtagcggcg gtggcggtag cggcggtggc ggtagcgcac tagtgctgca gtgtatcaag 1500

gttaacaact gggatttatt cttcagcccg agtgaagaca acttcaccaa cgacctgaac 1560

aaaggtgaag aaatcacctc agatactaac atcgaagcag ccgaagaaaa catctcgctg 1620

gacctgatcc agcagtacta cctgaccttt aatttcgaca acgagccgga aaacatttct 1680

atcgaaaacc tgagctctga tatcatcggc cagctggaac tgatgccgaa catcgaacgt 1740

ttcccaaacg gtaaaaagta cgagctggac aaatatacca tgttccacta cctgcgcgcg 1800

caggaatttg aacacggcaa atcccgtatc gcactgacta actccgttaa cgaagctctg 1860

ctcaacccgt cccgtgtata caccttcttc tctagcgact acgtgaaaaa ggtcaacaaa 1920

gcgactgaag ctgcaatgtt cttgggttgg gttgaacagc ttgtttatga ttttaccgac 1980

gagacgtccg aagtatctac taccgacaaa attgcggata tcactatcat catcccgtac 2040

atcggtccgg ctctgaacat tggcaacatg ctgtacaaag acgacttcgt tggcgcactg 2100

atcttctccg gtgcggtgat cctgctggag ttcatcccgg aaatcgccat cccggtactg 2160

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aacgcgctga gcaaacgtaa cgaaaaatgg gatgaagttt acaaatatat cgtgaccaac 2280

tggctggcta aggttaatac tcagatcgac ctcatccgca aaaaaatgaa agaagcactg 2340

gaaaaccagg cggaagctac caaggcaatc attaactacc agtacaacca gtacaccgag 2400

gaagaaaaaa acaacatcaa cttcaacatc gacgatctgt cctctaaact gaacgaatcc 2460

atcaacaaag ctatgatcaa catcaacaag ttcctgaacc agtgctctgt aagctatctg 2520

atgaactcca tgatcccgta cggtgttaaa cgtctggagg acttcgatgc gtctctgaaa 2580

gacgccctgc tgaaatacat ttacgacaac cgtggcactc tgatcggtca ggttgatcgt 2640

ctgaaggaca aagtgaacaa taccttatcg accgacatcc cttttcagct cagtaaatat 2700

gtcgataacc aacgcctttt gtccactcta gactag 2736

<210> 85

<211> 911
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 85

Gly Ser Met Pro Ile Thr Ile Asn Asn Phe Arg Tyr Ser Asp Pro Val
1 5 10 15

Asn Asn Asp Thr Ile Ile Met Met Glu Pro Pro Tyr Cys Lys Gly Leu
20 25 30

Asp Ile Tyr Tyr Lys Ala Phe Lys Ile Thr Asp Arg Ile Trp Ile Val
35 40 45

Pro Glu Arg Tyr Glu Phe Gly Thr Lys Pro Glu Asp Phe Asn Pro Pro
50 55 60

Ser Ser Leu Ile Glu Gly Ala Ser Glu Tyr Tyr Asp Pro Asn Tyr Leu
65 70 75 80

Arg Thr Asp Ser Asp Lys Asp Arg Phe Leu Gln Thr Met Val Lys Leu
85 90 95

Phe Asn Arg Ile Lys Asn Asn Val Ala Gly Glu Ala Leu Leu Asp Lys
100 105 110

Ile Ile Asn Ala Ile Pro Tyr Leu Gly Asn Ser Tyr Ser Leu Leu Asp
115 120 125

Lys Phe Asp Thr Asn Ser Asn Ser Val Ser Phe Asn Leu Leu Glu Gln
130 135 140

Asp Pro Ser Gly Ala Thr Thr Lys Ser Ala Met Leu Thr Asn Leu Ile
145 150 155 160

Ile Phe Gly Pro Gly Pro Val Leu Asn Lys Asn Glu Val Arg Gly Ile
165 170 175

Val Leu Arg Val Asp Asn Lys Asn Tyr Phe Pro Cys Arg Asp Gly Phe
180 185 190

Gly Ser Ile Met Gln Met Ala Phe Cys Pro Glu Tyr Val Pro Thr Phe
195 200 205

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Asp Asn Val Ile Glu Asn Ile Thr Ser Leu Thr Ile Gly Lys Ser Lys
    210                 215                 220

Tyr Phe Gln Asp Pro Ala Leu Leu Leu Met His Glu Leu Ile His Val
225                 230                 235                 240

Leu His Gly Leu Tyr Gly Met Gln Val Ser Ser His Glu Ile Ile Pro
                245                 250                 255

Ser Lys Gln Glu Ile Tyr Met Gln His Thr Tyr Pro Ile Ser Ala Glu
            260                 265                 270

Glu Leu Phe Thr Phe Gly Gly Gln Asp Ala Asn Leu Ile Ser Ile Asp
        275                 280                 285

Ile Lys Asn Asp Leu Tyr Glu Lys Thr Leu Asn Asp Tyr Lys Ala Ile
    290                 295                 300

Ala Asn Lys Leu Ser Gln Val Thr Ser Cys Asn Asp Pro Asn Ile Asp
305                 310                 315                 320

Ile Asp Ser Tyr Lys Gln Ile Tyr Gln Gln Lys Tyr Gln Phe Asp Lys
                325                 330                 335

Asp Ser Asn Gly Gln Tyr Ile Val Asn Glu Asp Lys Phe Gln Ile Leu
            340                 345                 350

Tyr Asn Ser Ile Met Tyr Gly Phe Thr Glu Ile Glu Leu Gly Lys Lys
        355                 360                 365

Phe Asn Ile Lys Thr Arg Leu Ser Tyr Phe Ser Met Asn His Asp Pro
    370                 375                 380

Val Lys Ile Pro Asn Leu Leu Asp Asp Thr Ile Tyr Asn Asp Thr Glu
385                 390                 395                 400

Gly Phe Asn Ile Glu Ser Lys Asp Leu Lys Ser Glu Tyr Lys Gly Gln
                405                 410                 415

Asn Met Arg Val Asn Thr Asn Ala Phe Arg Asn Val Asp Gly Ser Gly
            420                 425                 430

Leu Val Ser Lys Leu Ile Gly Leu Cys Val Asp Gly Ile Ile Thr Ser
        435                 440                 445

Lys Thr Lys Ser Leu Ile Glu Gly Arg Phe Gly Gly Phe Thr Gly Ala
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    450                 455                 460

Arg Lys Ser Ala Arg Lys Arg Lys Asn Gln Ala Leu Ala Gly Gly Gly
465                 470                 475                 480

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Val Leu
                485                 490                 495

Gln Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu
            500                 505                 510

Asp Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp
        515                 520                 525

Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln
    530                 535                 540

Gln Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser
545                 550                 555                 560

Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro
                565                 570                 575

Asn Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr
            580                 585                 590

Thr Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser
        595                 600                 605

Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser
    610                 615                 620

Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys
625                 630                 635                 640

Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr
                645                 650                 655

Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala
            660                 665                 670

Asp Ile Thr Ile Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly
        675                 680                 685

Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly
    690                 695                 700
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Ala Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu
705 710 715 720

Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val
725 730 735

Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu
740 745 750

Val Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln
755 760 765

Ile Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala
770 775 780

Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu
785 790 795 800

Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys
805 810 815

Leu Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu
820 825 830

Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly
835 840 845

Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu
850 855 860

Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg
865 870 875 880

Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln
885 890 895

Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Leu Asp
900 905 910

<210> 86
<211> 180
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 86
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tcagcgcgta aacgtaagaa ccaggcgcta gcgggcggtg gcggtagcgg cggtggcggt 120

agcggcggtg gcggtagcgc actagtgctg cagacgcacg gtctagaatg ataaaagctt 180

<210> 87
<211> 2715
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 87
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aaaaacatcc tgtacctgga tacccatctg aataccctgg cgaacgaacc ggaaaaagcg 120

tttcgtatca ccggcaacat ttgggttatt ccggatcgtt ttagccgtaa cagcaacccg 180

aatctgaata aaccgccgcg tgttaccagc ccgaaaagcg gttattacga tccgaactat 240

ctgagcaccg atagcgataa agataccttc ctgaaagaaa tcatcaaact gttcaaacgc 300

atcaacagcc gtgaaattgg cgaagaactg atctatcgcc tgagcaccga tattccgttt 360

ccgggcaaca acaacacccc gatcaacacc tttgatttcg atgtggattt caacagcgtt 420

gatgttaaaa cccgccaggg taacaattgg gtgaaaaccg gcagcattaa cccgagcgtg 480

attattaccg gtccgcgcga aaacattatt gatccggaaa ccagcacctt taaactgacc 540

aacaacacct ttgcggcgca ggaaggtttt ggcgcgctga gcattattag cattagcccg 600

cgctttatgc tgacctatag caacgcgacc aacgatgttg gtgaaggccg tttcagcaaa 660

agcgaatttt gcatggaccc gatcctgatc ctgatgcatg aactgaacca tgcgatgcat 720

aacctgtatg gcatcgcgat tccgaacgat cagaccatta gcagcgtgac cagcaacatc 780

ttttacagcc agtacaacgt gaaactggaa tatgcggaaa tctatgcgtt tggcggtccg 840

accattgatc tgattccgaa aagcgcgcgc aaatacttcg aagaaaaagc gctggattac 900

tatcgcagca ttgcgaaacg tctgaacagc attaccaccg cgaatccgag cagcttcaac 960

aaatatatcg gcgaatataa acagaaactg atccgcaaat atcgctttgt ggtggaaagc 1020

agcggcgaag ttaccgttaa ccgcaataaa ttcgtggaac tgtacaacga actgacccag 1080

atcttcaccg aatttaacta tgcgaaaatc tataacgtgc agaaccgtaa aatctacctg 1140

agcaacgtgt ataccccggt gaccgcgaat attctggatg ataacgtgta cgatatccag 1200

aacggcttta acatcccgaa aagcaacctg aacgttctgt ttatgggcca gaacctgagc 1260

tcgtaatccgg cgctgcgtaa agtgaacccg gaaaacatgc tgtacctgtt caccaaattt 1320

tgcgtcgacg cgattgatgg tcgttttggc ggtttcacgg gcgcacgcaa atcagcgcgt 1380

aaacgtaaga accaggcgct agcgggcggt ggcggtagcg gcggtggcgg tagcggcggt 1440

ggcggtagcg cactagtgct gcagtgtcgt gaactgctgg tgaaaaacac cgatctgccg 1500

tttattggcg atatcagcga tgtgaaaacc gatatcttcc tgcgcaaaga tatcaacgaa 1560

gaaaccgaag tgatctacta cccggataac gtgagcgttg atcaggtgat cctgagcaaa 1620

aacaccagcg aacatggtca gctggatctg ctgtatccga gcattgatag cgaaagcgaa 1680

attctgccgg gcgaaaacca ggtgttttac gataaccgta cccagaacgt ggattacctg 1740

aacagctatt actacctgga aagccagaaa ctgagcgata acgtggaaga ttttaccttt 1800

acccgcagca ttgaagaagc gctggataac agcgcgaaag tttacaccta ttttccgacc 1860

ctggcgaaca aagttaatgc gggtgttcag ggcggtctgt ttctgatgtg ggcgaacgat 1920

gtggtggaag atttcaccac caacatcctg cgtaaagata ccctggataa aatcagcgat 1980

gttagcgcga ttattccgta tattggtccg gcgctgaaca ttagcaatag cgtgcgtcgt 2040

ggcaatttta ccgaagcgtt tgcggttacc ggtgtgacca ttctgctgga agcgtttccg 2100

gaatttacca ttccggcgct gggtgcgttt gtgatctata gcaaagtgca ggaacgcaac 2160

gaaatcatca aaaccatcga taactgcctg gaacagcgta ttaaacgctg gaaagatagc 2220

tatgaatgga tgatgggcac ctggctgagc cgtattatca cccagttcaa caacatcagc 2280

taccagatgt acgatagcct gaactatcag gcgggtgcga ttaaagcgaa aatcgatctg 2340

gaatacaaaa aatacagcgg cagcgataaa gaaaacatca aaagccaggt tgaaaacctg 2400

aaaaacagcc tggatgtgaa aattagcgaa gcgatgaata acatcaacaa attcatccgc 2460

gaatgcagcg tgacctacct gttcaaaaac atgctgccga aagtgatcga tgaactgaac 2520

gaatttgatc gcaacaccaa agcgaaactg atcaacctga tcgatagcca caacattatt 2580

ctggtgggcg aagtggataa actgaaagcg aaagttaaca acagcttcca gaacaccatc 2640

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ttcaatctag actag 2715

<210> 88
<211> 904
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 88

Gly Ser Glu Phe Met Pro Ile Thr Ile Asn Asn Phe Asn Tyr Ser Asp

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Pro Val Asp Asn Lys Asn Ile Leu Tyr Leu Asp Thr His Leu Asn Thr
            20                  25                  30

Leu Ala Asn Glu Pro Glu Lys Ala Phe Arg Ile Thr Gly Asn Ile Trp
        35                  40                  45

Val Ile Pro Asp Arg Phe Ser Arg Asn Ser Asn Pro Asn Leu Asn Lys
    50                  55                  60

Pro Pro Arg Val Thr Ser Pro Lys Ser Gly Tyr Tyr Asp Pro Asn Tyr
65                  70                  75                  80

Leu Ser Thr Asp Ser Asp Lys Asp Thr Phe Leu Lys Glu Ile Ile Lys
                85                  90                  95

Leu Phe Lys Arg Ile Asn Ser Arg Glu Ile Gly Glu Glu Leu Ile Tyr
            100                 105                 110

Arg Leu Ser Thr Asp Ile Pro Phe Pro Gly Asn Asn Asn Thr Pro Ile
        115                 120                 125

Asn Thr Phe Asp Phe Asp Val Asp Phe Asn Ser Val Asp Val Lys Thr
    130                 135                 140

Arg Gln Gly Asn Asn Trp Val Lys Thr Gly Ser Ile Asn Pro Ser Val
145                 150                 155                 160

Ile Ile Thr Gly Pro Arg Glu Asn Ile Ile Asp Pro Glu Thr Ser Thr
                165                 170                 175

Phe Lys Leu Thr Asn Asn Thr Phe Ala Ala Gln Glu Gly Phe Gly Ala
            180                 185                 190

Leu Ser Ile Ile Ser Ile Ser Pro Arg Phe Met Leu Thr Tyr Ser Asn
        195                 200                 205

Ala Thr Asn Asp Val Gly Glu Gly Arg Phe Ser Lys Ser Glu Phe Cys
    210                 215                 220

Met Asp Pro Ile Leu Ile Leu Met His Glu Leu Asn His Ala Met His
225                 230                 235                 240

Asn Leu Tyr Gly Ile Ala Ile Pro Asn Asp Gln Thr Ile Ser Ser Val
                245                 250                 255
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Thr Ser Asn Ile Phe Tyr Ser Gln Tyr Asn Val Lys Leu Glu Tyr Ala
            260                 265                 270

Glu Ile Tyr Ala Phe Gly Gly Pro Thr Ile Asp Leu Ile Pro Lys Ser
        275                 280                 285

Ala Arg Lys Tyr Phe Glu Glu Lys Ala Leu Asp Tyr Tyr Arg Ser Ile
    290                 295                 300

Ala Lys Arg Leu Asn Ser Ile Thr Thr Ala Asn Pro Ser Ser Phe Asn
305                 310                 315                 320

Lys Tyr Ile Gly Glu Tyr Lys Gln Lys Leu Ile Arg Lys Tyr Arg Phe
                325                 330                 335

Val Val Glu Ser Ser Gly Glu Val Thr Val Asn Arg Asn Lys Phe Val
            340                 345                 350

Glu Leu Tyr Asn Glu Leu Thr Gln Ile Phe Thr Glu Phe Asn Tyr Ala
        355                 360                 365

Lys Ile Tyr Asn Val Gln Asn Arg Lys Ile Tyr Leu Ser Asn Val Tyr
    370                 375                 380

Thr Pro Val Thr Ala Asn Ile Leu Asp Asp Asn Val Tyr Asp Ile Gln
385                 390                 395                 400

Asn Gly Phe Asn Ile Pro Lys Ser Asn Leu Asn Val Leu Phe Met Gly
                405                 410                 415

Gln Asn Leu Ser Arg Asn Pro Ala Leu Arg Lys Val Asn Pro Glu Asn
            420                 425                 430

Met Leu Tyr Leu Phe Thr Lys Phe Cys Val Asp Ala Ile Asp Gly Arg
        435                 440                 445

Phe Gly Gly Phe Thr Gly Ala Arg Lys Ser Ala Arg Lys Arg Lys Asn
    450                 455                 460

Gln Ala Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Ala Leu Val Leu Gln Cys Arg Glu Leu Leu Val Lys Asn
                485                 490                 495
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Thr Asp Leu Pro Phe Ile Gly Asp Ile Ser Asp Val Lys Thr Asp Ile
            500                 505                 510

Phe Leu Arg Lys Asp Ile Asn Glu Glu Thr Glu Val Ile Tyr Tyr Pro
        515                 520                 525

Asp Asn Val Ser Val Asp Gln Val Ile Leu Ser Lys Asn Thr Ser Glu
    530                 535                 540

His Gly Gln Leu Asp Leu Leu Tyr Pro Ser Ile Asp Ser Glu Ser Glu
545                 550                 555                 560

Ile Leu Pro Gly Glu Asn Gln Val Phe Tyr Asp Asn Arg Thr Gln Asn
                565                 570                 575

Val Asp Tyr Leu Asn Ser Tyr Tyr Tyr Leu Glu Ser Gln Lys Leu Ser
            580                 585                 590

Asp Asn Val Glu Asp Phe Thr Phe Thr Arg Ser Ile Glu Glu Ala Leu
        595                 600                 605

Asp Asn Ser Ala Lys Val Tyr Thr Tyr Phe Pro Thr Leu Ala Asn Lys
    610                 615                 620

Val Asn Ala Gly Val Gln Gly Gly Leu Phe Leu Met Trp Ala Asn Asp
625                 630                 635                 640

Val Val Glu Asp Phe Thr Thr Asn Ile Leu Arg Lys Asp Thr Leu Asp
                645                 650                 655

Lys Ile Ser Asp Val Ser Ala Ile Ile Pro Tyr Ile Gly Pro Ala Leu
            660                 665                 670

Asn Ile Ser Asn Ser Val Arg Arg Gly Asn Phe Thr Glu Ala Phe Ala
        675                 680                 685

Val Thr Gly Val Thr Ile Leu Leu Glu Ala Phe Pro Glu Phe Thr Ile
    690                 695                 700

Pro Ala Leu Gly Ala Phe Val Ile Tyr Ser Lys Val Gln Glu Arg Asn
705                 710                 715                 720

Glu Ile Ile Lys Thr Ile Asp Asn Cys Leu Glu Gln Arg Ile Lys Arg
                725                 730                 735
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Trp Lys Asp Ser Tyr Glu Trp Met Met Gly Thr Trp Leu Ser Arg Ile
740 745 750

Ile Thr Gln Phe Asn Asn Ile Ser Tyr Gln Met Tyr Asp Ser Leu Asn
755 760 765

Tyr Gln Ala Gly Ala Ile Lys Ala Lys Ile Asp Leu Glu Tyr Lys Lys
770 775 780

Tyr Ser Gly Ser Asp Lys Glu Asn Ile Lys Ser Gln Val Glu Asn Leu
785 790 795 800

Lys Asn Ser Leu Asp Val Lys Ile Ser Glu Ala Met Asn Asn Ile Asn
805 810 815

Lys Phe Ile Arg Glu Cys Ser Val Thr Tyr Leu Phe Lys Asn Met Leu
820 825 830

Pro Lys Val Ile Asp Glu Leu Asn Glu Phe Asp Arg Asn Thr Lys Ala
835 840 845

Lys Leu Ile Asn Leu Ile Asp Ser His Asn Ile Ile Leu Val Gly Glu
850 855 860

Val Asp Lys Leu Lys Ala Lys Val Asn Asn Ser Phe Gln Asn Thr Ile
865 870 875 880

Pro Phe Asn Ile Phe Ser Tyr Thr Asn Asn Ser Leu Leu Lys Asp Ile
885 890 895

Ile Asn Glu Tyr Phe Asn Leu Asp
900